The American Journal of Medicine

September 1949

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The American Journal of Medicine

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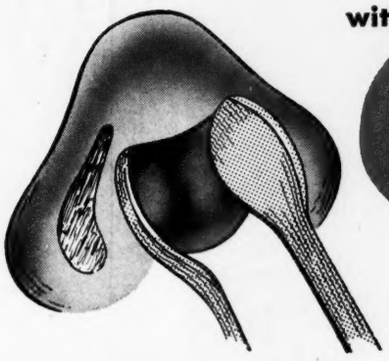

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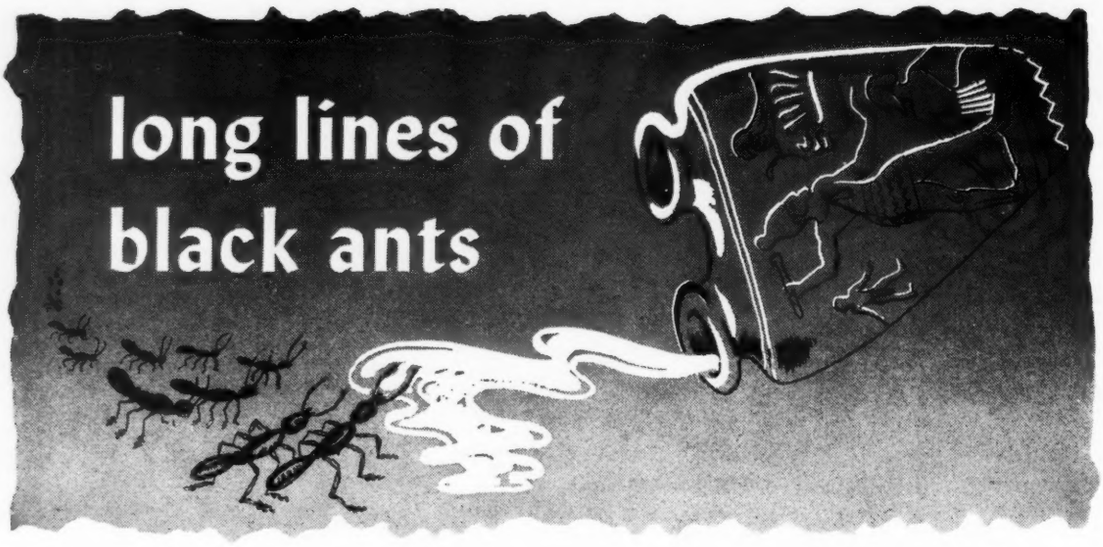

Long lines of black ants attracted to madhumeha, "honey urine," led the ancient Hindu wise men to observe and recognize diabetic urine, which they described as "astringent, sweet, white and sharp." Avid insects became an acknowledged means of diagnosis. Almost equally primitive methods of urine-sugar detection remained in effect for a score or more of centuries, until modern copper reduction tests were perfected, refined and simplified.

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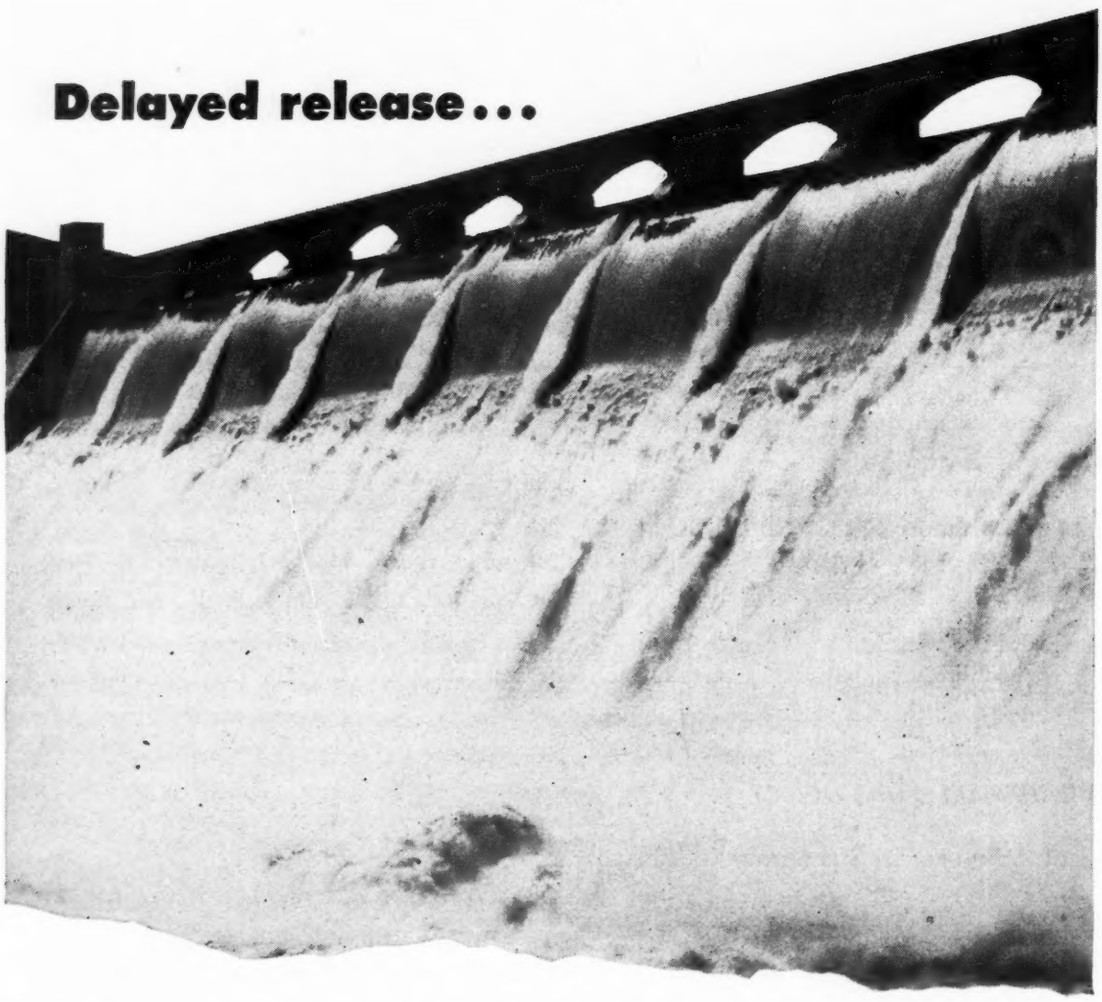

Just as a great dam stores and releases water only as fast as the fertile lands below can utilize it, so does Alhydrox* adsorb antigens and release them *slowly* from tissue after injection. This gives the effect of continuous small doses.

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Special Feature

Case Reports

General Information

THE AMERICAN JOURNAL OF MEDICINE extends an invitation to the profession for original releases on clinical investigations, clinical reviews, case reports and articles designed for postgraduate teaching.

Articles are accepted for publication with the understanding that they are original contributions never previously published. All manuscripts are subject to editorial modification, and upon acceptance become the property of THE AMERICAN JOURNAL OF MEDICINE.

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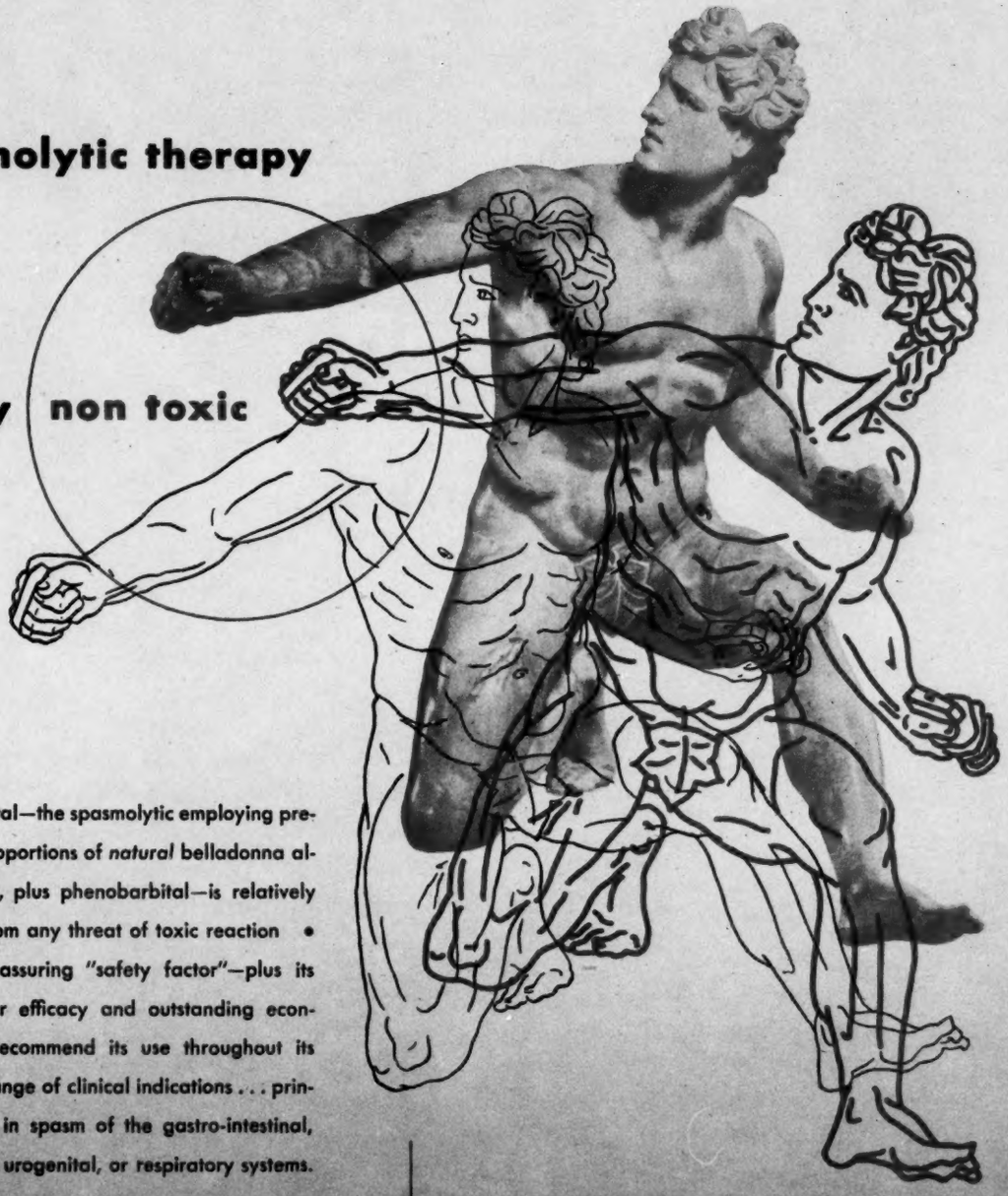
spasmolytic therapy

safely non toxic



Donnatal—the spasmolytic employing precise proportions of *natural* belladonna alkaloids, plus phenobarbital—is relatively free from any threat of toxic reaction • This reassuring "safety factor"—plus its superior efficacy and outstanding economy—recommend its use throughout its wide range of clinical indications . . . principally in spasm of the gastro-intestinal, biliary, urogenital, or respiratory systems.

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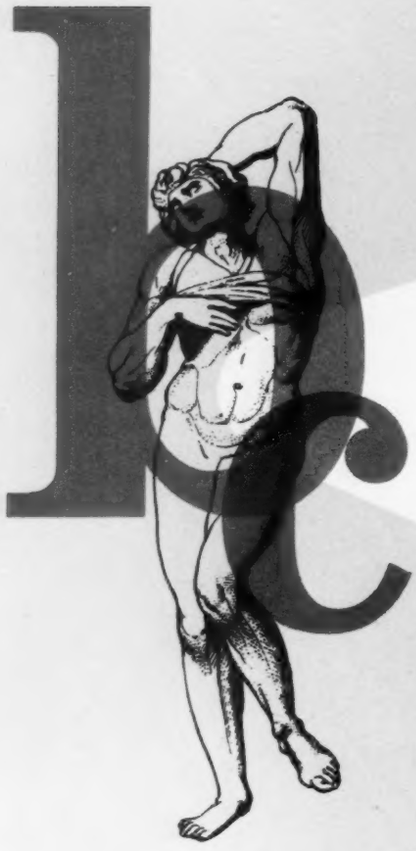

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vitamin levels

each capsule contains:

Thiamine Hydrochloride (B_1)	15 mg.
Riboflavin (B_2)	10 mg.
Calcium Pantothenate	10 mg.
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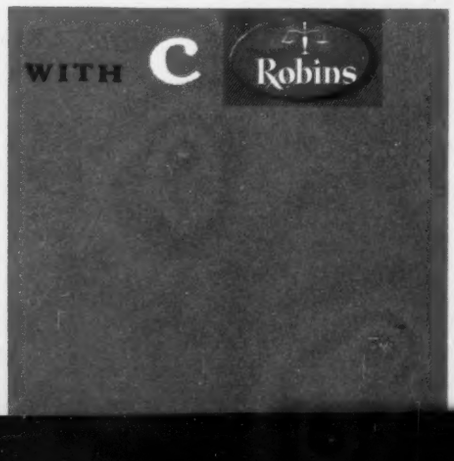
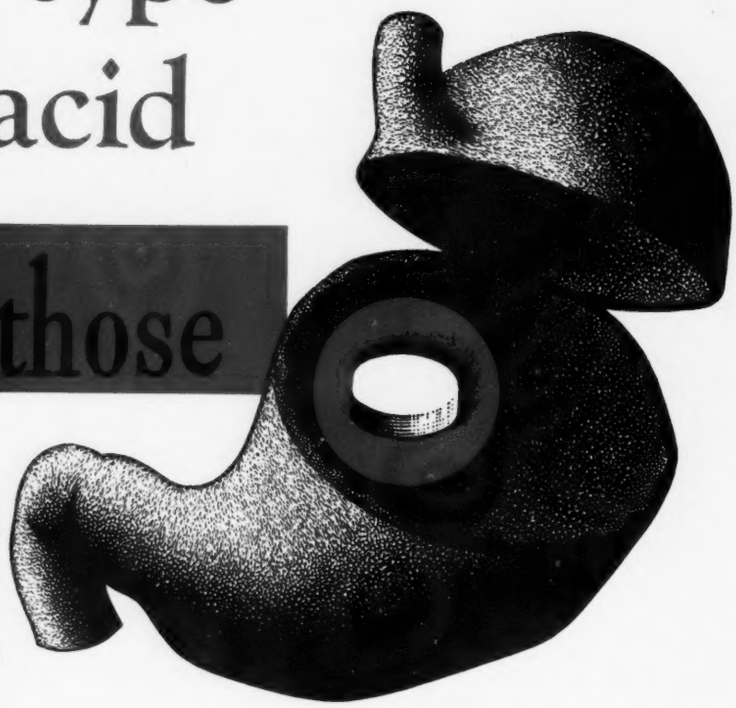


New type antacid

Carmethose



for better management of peptic ulcer

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1. *Non-constipating*—hydrophilic gel promotes normal elimination.[1, 2]
2. *Reduction of acidity in two ways*—prompt action by ion exchange is followed by classical buffering action.
3. *Palatable*—small, easily swallowed tablets and pleasantly flavored liquid—preferred by patients.[2]

Advantages over soluble alkalis:

1. *No acid rebound*—effectively inhibits acid-pepsin activity, with no secondary hypersecretion.
2. *Protective coating*—mucin-like gel is rapidly formed and clings to ulcer crater and gastric mucosa.
3. *Non-systemic*—cannot disturb acid-base balance because it is non-absorbable.

1. Brick, I.B.: Amer. J. Dig. Dis., *In Press* 2. Bralow, Spellberg & Necheles: Scientific Exhibit #1112, A.M.A. Annual Session 1949

announcing another Robins' achievement

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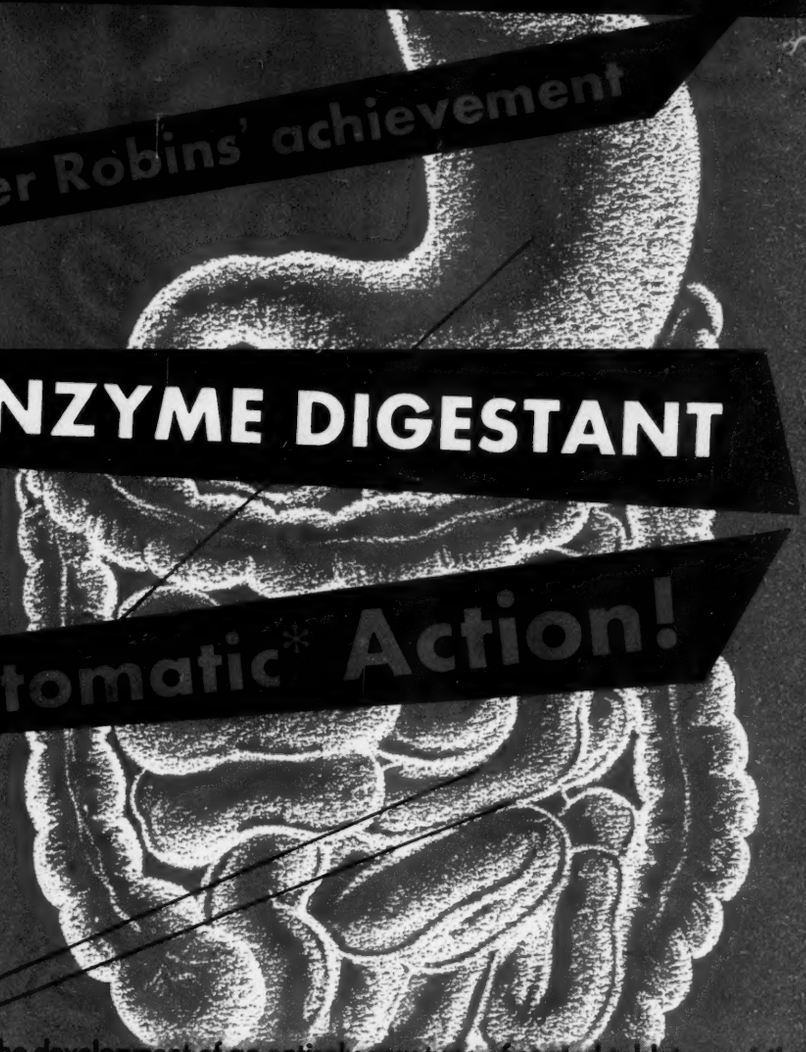
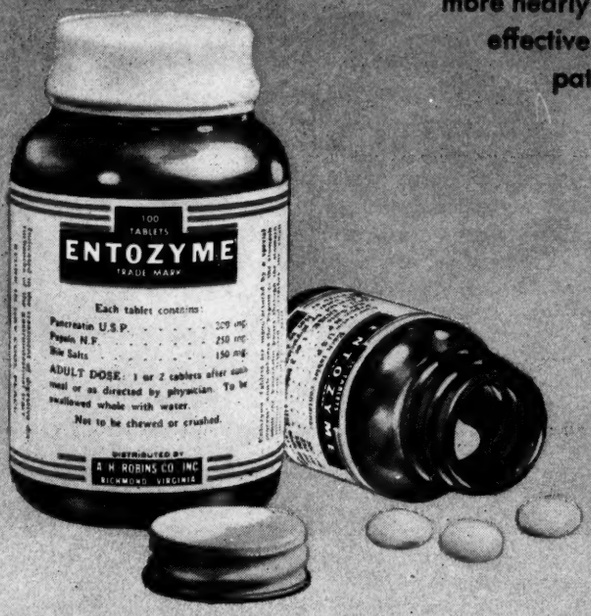


Gastrically soluble outer shell contains pepsin; enterically coated core contains pancreatin and bile salts.

By the development of an entirely new type of coated tablet, consisting of a gastrically soluble outer shell containing pepsin, and an enterically coated core containing pancreatin and bile salts—Robins (with their new product Entozyme) now makes it possible to release these three important digestants *in fully active form* to that part of the gastrointestinal tract where pH conditions for optimum activity prevail. Clinical research[1] indicates that Entozyme's greatest field of usefulness is in chronic cholecystitis, post-cholecystectomy syndrome, subtotal gastrectomy, infectious hepatitis, pancreatitis and chronic dyspepsia—where its unique selective therapy restores more nearly physiological conditions in the gastrointestinal tract. It is also highly effective in nausea, anorexia, belching, flatulence and pyrosis. In peptic ulcer patients, too, pancreatin-pepsin therapy has produced excellent results.[2]



FORMULA: Each specially constructed tablet contains Pancreatin, U.S.P., 300 mg.; Pepsin, N.F., 250 mg.; Bile Salts, 150 mg.

DOSAGE: 1 or 2 tablets after each meal, or as directed by physician, without crushing or chewing.

SUPPLIED: Bottles of 25 and 100.

REFERENCES: 1. McGavack, T. H. and Klotz, S. D.: Bull. Flower Fifth Ave. Hosp., 9:61, 1946. 2. Weissberg, J., McGavack, T. H. and Boyd, Linn J.: Am. J. Digest. Dis., 15:332, 1948.

**A coined word to describe the unique mechanical action of Entozyme Tablet—whereby pepsin is released only in the stomach, and pancreatin and bile salts only in the small intestine.*

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ENTOZYME

Robins

"Results with Chlorophyll Therapy in 40 Cases of Dermatoses"

Excerpts from a clinical paper by W. D. Langley, M. D., and W. S. Morgan, M. D., published in The Pennsylvania Medical Journal, 51:44, 1947. This clinical investigation was conducted in the Guthrie Clinic and Robert Packer Hospital, Sayre, Pa.

The following synopsis provides physicians a convenient review of the clinical experience of Drs. Langley and Morgan with Chloresium chlorophyll therapy in the treatment of acute and chronic dermatoses. It quotes their reasons for undertaking the investigation . . . describes the subjective and objective effects of the treatment . . . and summarizes the final results. This report is one of an extensive series of published papers on Chloresium chlorophyll therapy; reprints are available on request.

Why this investigation was undertaken

"Following the recent experimental work on water-soluble chlorophyll proving it to be a tissue stimulant which resulted in the suggestion that this drug might be found of value in the treatment of osteomyelitis, burns, and chronic ulcers, it was thought worthwhile to employ this substance in a series of such cases in an attempt to corroborate clinically the experimental findings. It was while this series† was in progress that we first became aware of the value of water-soluble chlorophyll* in the treatment of certain dermatoses . . .

"Chlorophyll (Chloresium) was used more or less in desperation when other measures had failed to relieve the subjective symptoms and objective manifestations of several cases of dermatoses of varied type. We knew from our own previous experience and from the literature that chlorophyll was bland in its effect on the skin. We did not anticipate in any measure, however, the degree of beneficial effect produced by chlorophyll . . .

Selection of cases and controls

"During a period of six months, from February to July, 1946, we treated 40 dermatologic cases, the majority of which had proved highly resistant to all previous treatment (see Table) . . .

"Eight patients having bilateral involvement were used as control cases. In each instance one extremity showed decided improvement upon treatment with water-soluble chlorophyll, whereas signs and symptoms persisted as before in the extremity treated with substances other than chlorophyll, such as Burrow's solution, Calamine lotion, starch baths, and boric acid ointment or compresses.

"Five cases were treated with the water-soluble ointment base alone, but were not improved. These later responded to chlorophyll therapy.

Relief of itching and burning

"One of the most gratifying results of treatment with water-soluble chlorophyll was its ability to relieve itching and burning. This effect was observed almost immediately and was usually sustained for ten or twelve hours after the initial applications.

Objective results

"The objective response seen over the involved areas proved to be no less dramatic than the palliation of symptoms aforedescribed. In many of the acute cases, areas which were highly erythematous, swollen, and weeping before application of water-soluble chlorophyll ointment were found to be greatly improved within ten to twelve hours. The absence of oozing after this period of time was most impressive. . . . Skin tenderness which in some of our cases had been severe was relieved overnight . . .

†The favorable findings from this study were presented (in a report "Treatment of Chronic Ulcers with Chlorophyll," in the Am. J. Surgery, April, 1948.)

*The water-soluble chlorophyll preparations used in this study were supplied by Rystan Company, Inc., Mt. Vernon, N. Y. They are marketed under the name "Chloresium" Solution [Plain] and Ointment.

SUMMARY TABLE

Diagnosis	No. of Cases	Duration	Previous Treatment	Results from Water-Soluble Chlorophyll Ointment	Statistics and Healing Time
Contact dermatitis	8	Two weeks to eighteen months	Cold boric acid and starch wet dressings; calamine lotions	Relief of itching in all cases; progressive objective improvement; decreased weeping, erythema, edema in acute cases; in chronic type, there was softening of skin and loss of lichenification; removal of crusts	All cases clinically cured: 5 within 10 days, 2 within 2 weeks, 1 within 1 month
Stasis dermatitis	13	One to eighteen months	Cold boric acid and starch wet dressings; penicillin ointment and bland ointments	Relief of itching and burning in all cases; progressive objective improvements	12 cases clinically cured: 6 within 10 days, 5 within 3 weeks, 1 within 6 weeks. No objective improvement in 1 case
Neurodermatitis	5	Three to eighteen months	Cold boric acid and starch wet dressings; x-rays, ultraviolet radiations, and bland ointments	Relief of itching and burning in all cases; diminished erythema, weeping, edema, crusting	All cases showed sustained improvement; 3 cases clinically cured within 2 weeks; 2 cases showed much improvement
Seborrheic dermatitis	3	Two weeks to one year	Cold wet dressings; penicillin ointment (one case, no previous treatment)	Relief of itching; diminished erythema, edema, weeping, crusting	All cases clinically cured within 2 weeks; 1 case within 2 days
Exfoliative dermatitis	2	Twelve to eighteen months	Zinc oxide; penicillin ointment; cold wet dressings	Diminished erythema, edema, weeping, scaling, crusting	Both cases clinically cured: 1 case within 2 weeks
Infantile eczema	2	One to three months	Boric acid ointment and penicillin ointment	Relief of itching; diminished erythema, weeping, crusting	Both cases clinically cured: 1 case within 1 week
Sycosis vulgaris	3	Two weeks to eight years	Penicillin ointment; x-rays	Relief of itching; diminished erythema, weeping, crusting	2 cases improved; 1 showed no objective improvement
Pyogenic fungus	1	Six months	Local applications of unknown type	Good	Healed in 7 days
Nummular eczema	1	Six months	Local applications	Poor	None
Psoriasis	1	Twelve years	Numerous local applications	Good symptomatic relief	No effect on lesions in 30 days
Moniliasis of vulva	1	Three years	X-ray therapy; estrogens; antipruritic application	Relief of itching and burning; was dramatic in 48 hours	Almost complete healing in 2½ mos.

"In no patient in this series of dermatologic problems treated with water-soluble chlorophyll has there been any evidence of toxicity or allergic reaction."

CONCLUSIONS

"Of 40 cases treated with water-soluble chlorophyll (Chloresium), all experienced relief of itching and burning. Thirty-six cases or 90 per cent showed decided improvement objectively. Four or 10 per cent were not improved.

"Of the 36 cases showing response to treatment with chlorophyll, 32 or 88.8 per cent have been completely relieved of the present attack. Four continue to improve under chlorophyll therapy.

"Of the 40 cases, 31 or 77.5 per cent had been active for one month or longer. Nine cases varied in duration from one to three weeks."

compare

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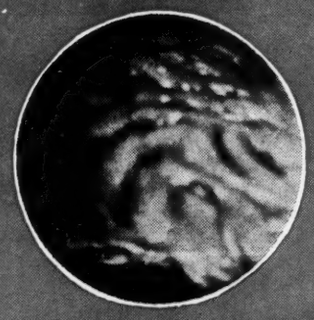
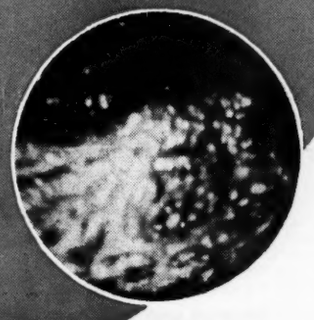


Gastrophotograph of mucosa coated by Resinat.



Gastrophotograph of mucosa coated by other substance.

Weiss, S., Espinal, R.B. & Weiss, J.: Therapeutic Application of Anion Exchange Resins in the Treatment of Peptic Ulcer, Review of Gastroenterology, 16:501-509, June, 1949.

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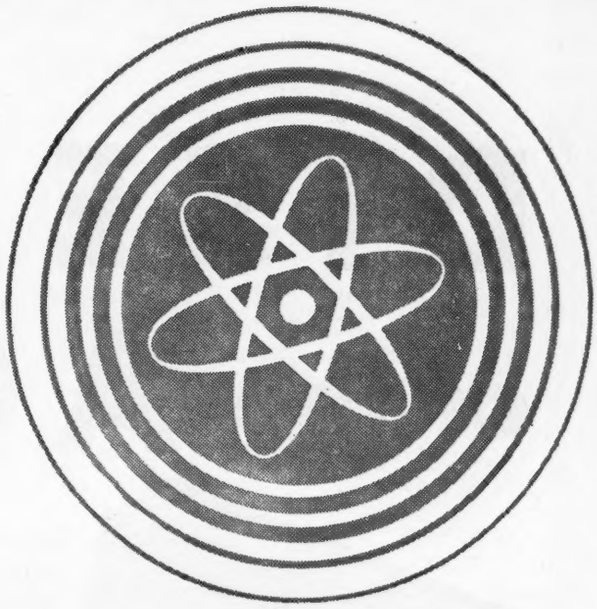
BOOK SECTION

Reading maketh a full man,
conference a ready man, and
writing an exact man.

—Bacon

THE ATOM KNOCKS AT THE DOCTOR'S DOOR!



Atomic Medicine

(RADIOACTIVITY IN PEACE AND WAR)

C. F. BEHRENS, M.D.

Captain, MC, U.S. Navy; Director, Atomic Defense Division, Bureau of Medicine and Surgery

EDITOR

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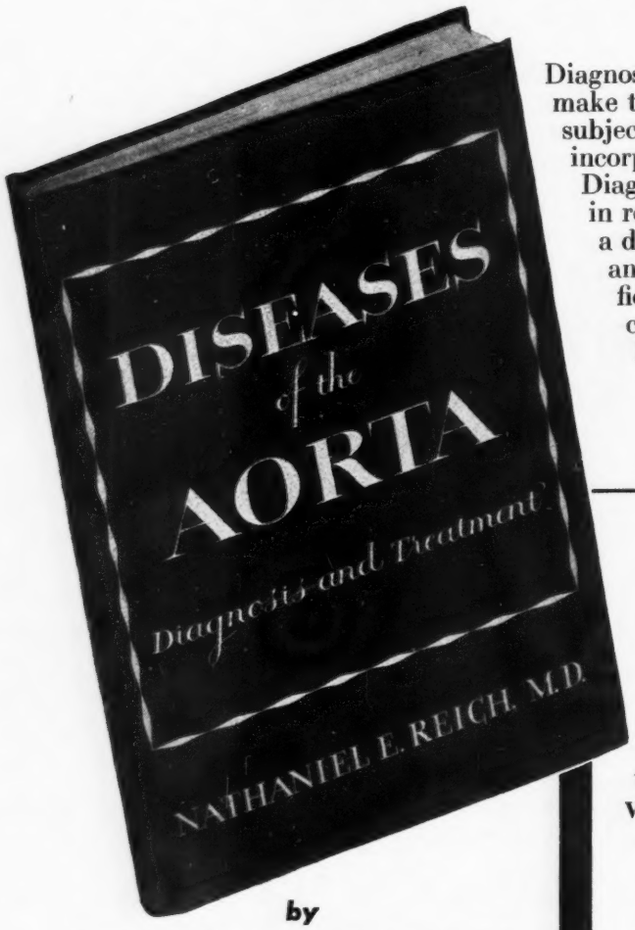
DISEASES of the AORTA



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by

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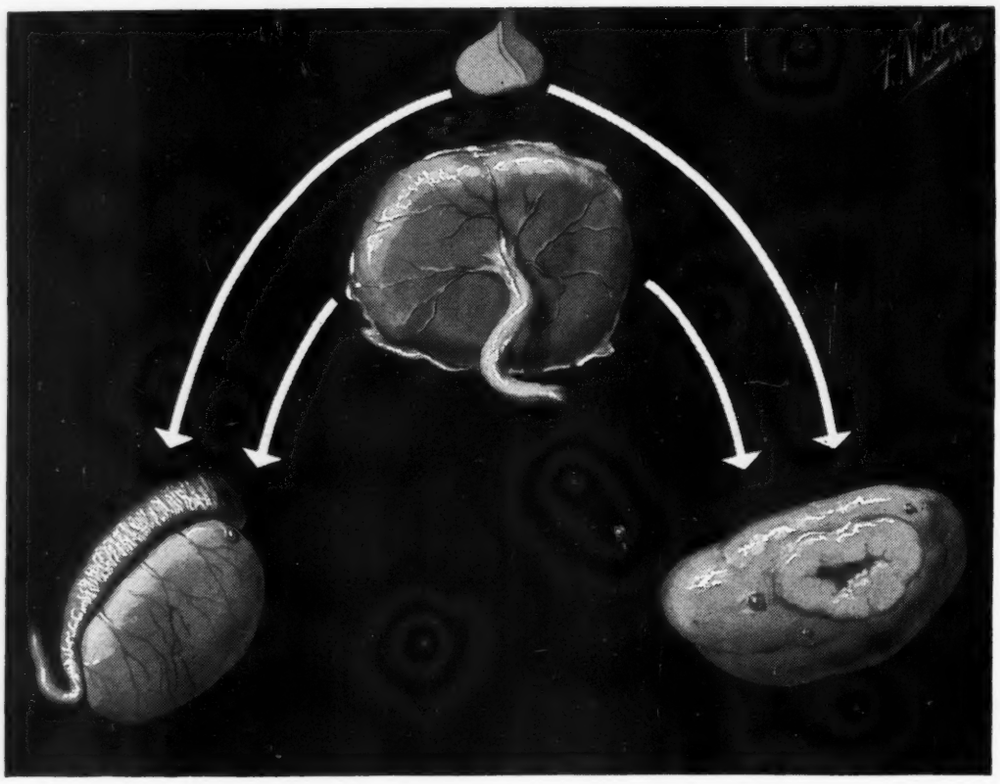

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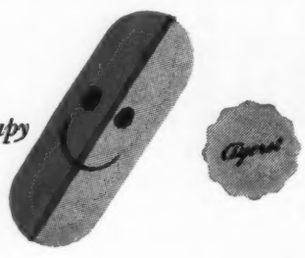

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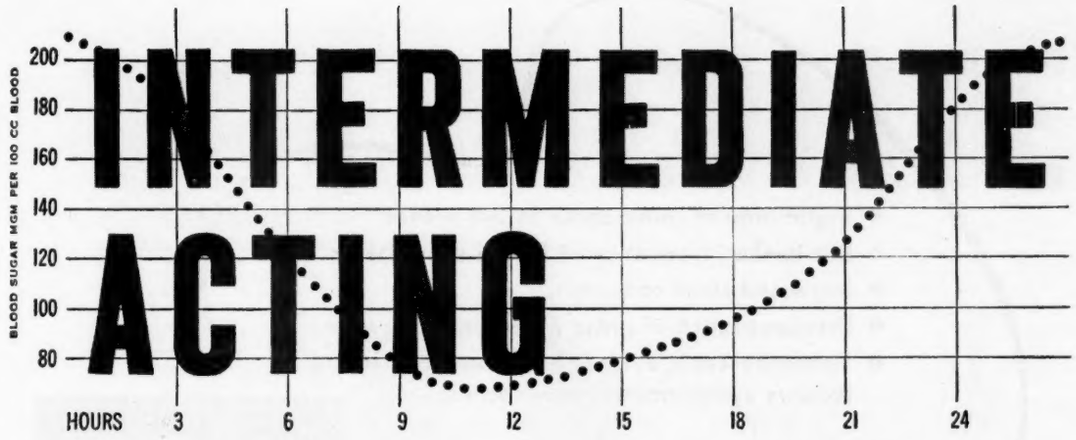

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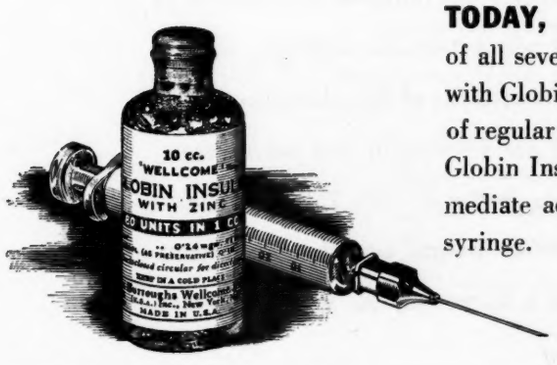

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1. Rohr, J.H., and Colwell, A.R.: Arch. Int. Med. 82:54, 1948.
2. Ibid Proc. Am. Diabetes Assn. 8:37, 1948.

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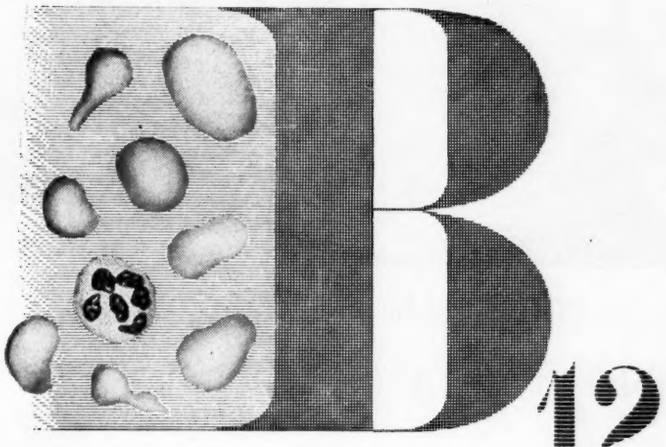

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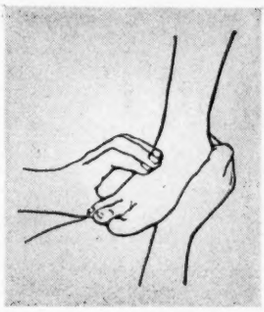

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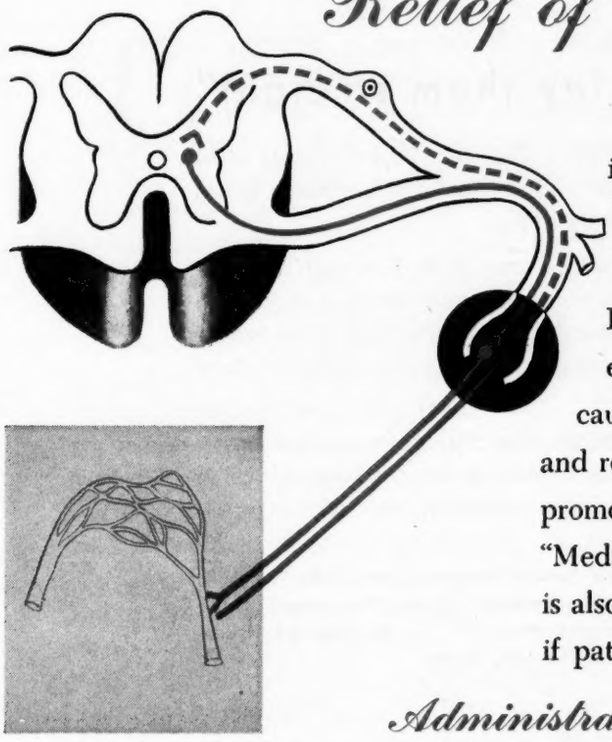

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The American Journal of Medicine

VOL. VII SEPTEMBER, 1949 No. 3

Editorial

Disinfection of the Air with Triethylene Glycol Vapor

THE present premature large-scale commercialization of glycol vapors for prevention of acute respiratory disease, together with the accompanying propagation of much misinformation concerning the use and effects of this form of aerial disinfection, make it seem particularly appropriate to review our knowledge of the field. Furthermore, in the two and one-half years intervening since a previous summary of this subject,[1] considerable new information has been acquired.

Among the many chemical compounds which have been tested as vapors or mists for their lethal action on air-borne infectious particles triethylene glycol still remains the agent of choice for use in environments occupied by human beings. Germicidal concentrations of this vapor are odorless, tasteless, non-irritating, non-toxic, invisible and have no deleterious effect on walls, fabrics, books or other objects in the treated space. The presence of as little as 1 cc. of vaporized triethylene glycol in several hundred million cc. of air is, under laboratory conditions, highly lethal for the common respiratory bacteria, pathogenic and non-pathogenic, as well as for the viruses of influenza,[1] psittacosis and meningopneumonitis.[2] Other bacteria including Bacillus coli and subtilis (vegetative form), a number of common non-pathogens of the air and certain molds appear to be susceptible to the action of the vapor.[3] No reports have been made of such studies on air-borne tubercle bacilli. Naturally occurring dust-borne bacteria have been found to be much more resistant to the killing action of the vapor than are those experimentally dispersed into the air.

The recent development of certain quantitative technics for study of this subject has made possible much more precise experimentation, the results of which amplify previous knowledge of the activity of triethylene glycol vapor and provide new interpretations. First, fundamental to a more exact understanding of its germicidal effects was determination of the amounts of glycol vapor which could exist in the air at varying humidities and temperatures. By means of a suitable method devised for this particular purpose[4] curves were constructed indicating the saturation concentrations of triethylene glycol under conditions of relative humidity from 0 to 90 per cent and at temperatures from 20°C. to 29°C. It was found that increasing humidity resulted in

[1] ROBERTSON, O. H. New methods for the control of air-borne infection with especial reference to the use of triethylene glycol vapor. *Wisconsin M. J.*, 46: 311–317, 1947.

[2] ROSEBURY, T., MEIKLEJOHN, G., KINGSLAND, L. C. and BOLDT, M. H. Disinfection of clouds of meningopneumonitis and psittacosis viruses with triethylene glycol vapor. *J. Exper. Med.*, 85: 65–76, 1947.

[3] BIGG, E. and MELLODY, M. Fungicidal action of triethylene glycol. *J. Infect. Dis.*, 79: 45–56, 1946.

[4] PUCK, T. T. and WISE, H. Studies on vapor liquid equilibria. I. A new dynamic method for the determination of vapor pressure of liquids. *J. Phys. Chem.*, 50: 329–339, 1946.

a progressive although not straightline diminution in quantity of glycol vapor required to saturate the air. Raising the temperature was found to increase the capacity of the air to hold glycol.[5] With these data available chemical analyses of glycol-containing air could then be interpreted in relation to per cent saturation—a figure which has been found to be much more significant in respect to bactericidal effect than was the absolute quantity of glycol in the atmosphere.

Another important advance was the further development of the glycostat, or glycometer, an instrument for measuring and controlling the concentration of triethylene glycol vapor in the air.[6] This instrument is extremely sensitive, being capable of detecting as little as 1 microgram of glycol/L. of air under ordinary conditions of humidity and temperature and responds rapidly to changes in concentration of vapor. By means of attachment to a recording device the glycometer provides a continuous record of the concentration of glycol in the atmosphere in terms of per cent saturation. It can be used also to control the output of the glycol vaporizer. Unfortunately this apparatus is not yet commercially available.

Employing the glycostat in specially constructed experimental rooms in which atmospheres could be maintained at any desired temperature and relative humidity, a large series of observations has been made on the bactericidal and virucidal action of varying concentrations of glycol vapor under a wide range of environmental conditions. Optimum conditions for the rapid action of the glycol vapor at ordinary room temperatures were found to be relative humidities of 15 to 40 per cent and vapor saturations of 40 to 100 per cent. In such atmospheres freshly atomized bacteria were killed in two to three minutes; 80 per cent or more of them were destroyed in the first minute. At high relative humidities (60 to 80 per cent) the rate of action was much reduced but still appreciable. Likewise, at very low humidities (5 to 10 per cent) killing was somewhat retarded. The more nearly the concentration of the glycol vapor in the air approached the saturation value the more rapid the kill. However, the increase in effectiveness at levels about 70 per cent was slight.[7]

Observations of an analogous nature on influenza virus in which white mice were exposed to atmospheres containing freshly atomized virus and glycol vapors showed that the presence of the glycol in the air at saturations of 70 to 90 per cent afforded the mice complete protection against lethal concentrations of the virus. Protection was optimum at relative humidities of 15 to 40 or 50 per cent, as was the case with bactericidal activity of the glycol. However, at high humidities, 70 to 80 per cent, the glycol had relatively little effect as most of the test mice died even when the air was saturated or supersaturated with triethylene glycol. Under optimum conditions of humidity and glycol saturation the virucidal action of the vapor was found to be very rapid.[8]

Studies with dried bacteria in the form of droplet nuclei or as a fine dust made from desiccated saliva suspensions have shown them to be about as susceptible to the lethal action of triethylene glycol vapor as are freshly atomized suspensions. The importance of this finding lies in the fact that most pathogenic bacteria present in an infected atmosphere are probably in the dried state.[8]

These more recent observations bring out the fact that, in adequate concentrations, triethylene glycol vapor is effective over a wider range of relative humidities

[5] Wise, H. and Puck, T. T. The saturation concentrations of triethylene glycol vapor at various relative humidities and temperatures. *Science*, 105: 556–557, 1947.

[6] Puck, T. T. An automatic dewpoint meter for the determination of condensible vapors. *Rev. Scient. Instruments*, 19: 16–23, 1948.

[7] Lester, W., Robertson, O. H., Puck, T. T., Wise, H. and Smith, M. The rate of bactericidal action of triethylene glycol vapor on microorganisms dispersed into the air in small droplets. *Am. J. Hyg.*, to be published.

[8] Robertson, O. H., Lester, W. and Dunklin, E. Unpublished experiments.

than was formerly thought to be the case.* It has not been found possible, however, to sterilize the air of inhabited rooms. Numerous tests under a variety of conditions have shown that the air-borne bacterial population can be reduced by not more than 70 to 75 per cent and the rate of killing is much slower than in the case of atomized bacterial suspensions. Investigation of dust-borne bacteria (non-pathogens with rare exceptions) indicates that the reason for their relative insensitivity to the lethal effect of triethylene glycol vapor lies in the physical state of the bacterial particle which obviously differs from that of the glycol-sensitive micro-organisms desiccated under laboratory conditions.

The utilization of glycol vapor for purposes of aerial disinfection involves a number of considerations which may be outlined briefly as follows: since triethylene glycol has a very low vapor pressure (boiling point is 550°F.) heat is essential for vaporization. However, the temperature which can be employed for this purpose is limited by the fact that this glycol begins to decompose at temperatures far below its boiling point. These properties of triethylene glycol introduce very definite requirements for the design of vaporizers. In order to disperse sufficient glycol into the air extended evaporating surfaces must be employed. Heating of the pool or reservoir of glycol should be avoided. Certain glycol vaporizers commercially available embody these principles, others do not.

Continuous dispersion of the glycol vapor into the treated space is essential because of the constant loss of vapor from the air, due to invisible condensation on all surfaces (including dust in the air) and the exchange of air which goes on to some degree even when windows and doors are closed. This loss amounts to 70 to 90 per cent of the glycol vaporized.[8] Hence in order to secure and maintain adequate concentrations of glycol in the air it is necessary to vaporize usually four to five times the amount of triethylene glycol calculated to produce the desired concentration in a given space. When air exchange in the room is increased by opening of doors and windows, the glycol requirement is even higher.

Air currents are necessary for uniform dispersion of glycol vapor throughout the treated space. In moderate-sized rooms of several thousand cu. feet the natural convection currents are usually adequate for this purpose. In larger spaces an electric fan or two depending on the size and shape of the space to be glycolized accomplishes the desired result. Air conditioning systems offer the most satisfactory means of glycol vapor distribution.

Maintenance of an adequate concentration of triethylene glycol vapor in the atmosphere offers the principal problem in the field of practical application. Until glycostats become available the only means of knowing whether sufficient glycol vapor is present, aside from chemical determination, is to produce a slight fog. The presence of a mist, best determined by the Tyndall effect (from a focused flashlight) does not necessarily indicate saturation of the air. A beam may be detectable at any concentration above 50 per cent saturation depending on the dustiness of the air. However, the occurrence of a Tyndall beam under ordinary conditions indicates the presence of a germicidal concentration. The optimum concentrations in terms of per cent saturation probably lie between 60 and 80 per cent.

Prior to its use in environments inhabited by human beings, prolonged tests (twelve to eighteen months) for chronic toxicity were carried out on monkeys and rats exposed continuously to atmospheres saturated with triethylene glycol vapor. In none of this large group of animals nor in

* Certain earlier studies,[9] which indicated that dried bacteria were relatively unsusceptible to glycol vapor action at humidities below 30 per cent, were carried out before any means was available for measuring concentrations of triethylene glycol in the air. Subsequent developments have shown that the amounts of glycol used in those experiments which were calculated to saturate the air actually produced concentrations so low as to be almost negligible.

[9] ROBERTSON, O. H. Sterilization of air with glycol vapors. Harvey Lecture Series, 38: 227–234, 1942–43.

others receiving oral doses many hundreds of times the amount they could absorb from inhalation were any deleterious effects observed either during life or in histologic sections of the organs following sacrifice at termination of the experiments.[10] Subsequent to these tests thousands of individuals have resided in glycol-containing atmospheres, many of them continuously for months, without apparent disturbance. The presence of triethylene glycol vapor in the air offers no fire or explosive hazard.

Evidence of the effect of triethylene glycol vapor derived from practical application is as yet scanty. Tests of the lethal action of glycol vapor on pathogens demonstrable in the air have thus far been confined to observations on hemolytic streptococci. In hospital wards housing patients with streptococcal respiratory tract infections the dispersion of triethylene glycol vapor resulted in reduction of air-borne streptococci of approximately 70 per cent. However, when in addition to glycol, dust control measures (oiling of bedding and floors) were instituted, the reduction was increased to 95 per cent. These findings bring out the importance of dust suppression as an adjunct to the use of triethylene glycol vapor.[11]

The few studies that have been reported on the clinical effects of employing glycol vapor for the prevention of air-borne infection are much more difficult to evaluate. The results of these experiments which were carried on in hospitals and military barracks vary from marked reduction of infections in the glycolized area[12] to inconclusive effects.[13] Environmental conditions of the several tests differed markedly and it is quite likely that opportunities for the transmission of infection by routes other than the air likewise varied. This latter unknown, namely, the percentage of cases of the various diseases of the respiratory tract that are air-borne makes the evaluation of any control measure most difficult. In environments such as hospital wards adequately controlled tests of the effect of aerial disinfection on the incidence of diseases acquired by way of the respiratory tract must include rigid enforcement of ward technics intended to reduce the possibility of channels of infection other than through the air.

From the foregoing summary it is apparent that the usefulness of triethylene glycol vapor as a means of protection against respiratory infection remains to be determined. However, the fact that this vapor has been shown to be a potent aerial disinfectant, at least for freshly dispersed pathogens, indicates the worthwhileness of more clinical trials in a variety of environments. The kind of control employed in such tests will of necessity vary with the particular environment and will have to be planned for each type of population under study. It is only through an accumulation of results from controlled experiments of this kind that an evaluation of the procedure will be possible.

In conclusion, reference should be made to the nationwide sale of glycol vaporizers. Two recent editorials in medical periodicals[14,15] have dealt with this subject pointing out the unfortunate aspects of unrestrained exploitation of glycol vapors and the fact that the majority of the vaporizing devices on the market are completely unsatisfactory. A few mechanically sound and efficient vaporizers are being produced and it seems likely that some means of official certification of such apparatus will soon be available.

O. H. Robertson, M.D.

[10] Robertson, O. H., Lossli, C. G., Puck, T. T., Lemon, H. M., Wise, H. and Lester, W. Tests for the chronic toxicity of propylene glycol and triethylene glycol on monkeys and rats by vapor inhalation and oral administration. *J. Pharmacol. & Exper. Therap.*, 91: 52–76, 1947.

[11] Puck, T. T., Hamburger, M., Robertson, O. H. and Hurst, V. The effect of triethylene glycol vapor on air-borne beta hemolytic streptococci in hospital wards. II. The combined action of glycol vapor and dust control measures. *J. Infect. Dis.*, 76: 216–225, 1945.

[12] Robertson, O. H. Disinfection of air by germicidal vapors and mists. *Am. J. Pub. Health*, 36: 390–391, 1946.

[13] Loosli, C. G., Smith, M. H. D., Gauld, R., Robertson, O. H. and Puck, T. T. Control of cross infections in infants' wards by the use of triethylene glycol vapor. *Am. J. Pub. Health*, 37: 1385–1398, 1947.

[14] Commercial exploitation of glycol vaporizers. *Am. J. Pub. Health*, 39: 222–224, 1949.

[15] The sale of glycol vaporizers. *Cincinnati J. Med.*, April, 1949.

Clinical Studies

I. Electrophoretic, Nitrogen and Lipide Analyses of Plasma and Plasma Fractions of Healthy Young Men*

H. Rowland Pearsall, M.D. *and* Alfred Chanutin, Ph.D.

Charlottesville, Virginia

Cohn and his associates recently introduced technics[1] for large scale fraction of plasma. This procedure (method VI) has many advantages due to the relative simplicity of the method; fractions may be obtained by varying pH, ionic strength and ethanol concentrations at low temperatures. Information concerning the protein components of the fractions separated by method VI are available only for pooled Red Cross plasmas.[1,2]

In the present investigation this procedure was modified so that small amounts of human plasma could be fractionated into Fractions I, II + III, IV-1, IV-4 and V. Variations of the electrophoretic patterns and of the nitrogen and lipide contents of the plasma and the plasma fractions of healthy young men are presented and may serve as normal standards for studies in which fractionation procedures are utilized in the investigation of the plasma in diseased states.

METHODS

Approximately 50 ml. of blood were drawn before breakfast from thirty male students (twenty to thirty years of age); clotting was prevented with heparin. Each blood was centrifuged shortly after collection and the plasma was removed immediately. Approximately 4 to 5 ml. of plasma were needed for electrophoretic and chemical analyses and the remaining plasma (17 to 20 ml.) was fractionated by slight modifications of method VI[1] within a few hours.

The plasma was fractionated in a 100 ml., round bottom, Pyrex centrifuge tube. The ethanol (53.3 or 95 per cent) was measured from a Machlett autoburette which was connected by rubber tubing to a small reservoir immersed in a low temperature bath. The cold ethanol was added slowly with continuous stirring to the protein-containing solution which was maintained at low temperatures (0 to −5°). The pH and ionic strengths were adjusted essentially as previously described.[1] The ethanol was added before adjusting pH and ionic strength. The pH was determined on small volumes (0.3 ml.) of the ethanol-protein mixture with the aid of a microcup and a Beckman instrument.

The plasma was diluted (1:1) initially with sodium chloride solutions (ionic strength 0.14) containing about 4 ml. of phosphate buffer (pH 6.4, ionic strength 0.15). The addition of the buffer was essential for the maintenance of proper hydrogen ion concentrations in the precipitation of Fractions I and II + III. Shortly after precipitation each fraction was dissolved in saline and brought to 10 ml. in a volumetric flask. Aliquots were taken for electrophoretic nitrogen and lipide analyses.

The plasma and fraction solutions were dialyzed against a barbiturate buffer (pH 8.6, ionic strength 0.1). Electrophoresis was carried out in the Tiselius apparatus at 2°, the patterns being recorded by the method of Longsworth.[3] A microcell* with a capacity of 2 ml. was used to obtain the electrophoretic patterns. Electrophoresis was usually allowed to continue for ninety minutes with a current of 8 ma. Mobility calculations were based on the distance from the peak of salt effect (δ) to the peak of the

* Obtained from Pyrocell Co., N. Y.

* From the Biochemical Laboratory, University of Virginia Medical School, Charlottesville, Va. This work was made possible by a grant from the Office of Naval Research.

respective components. The areas of the ascending patterns were measured.

The total lipides of the plasma and fractions were extracted with hot acetone-absolute alcohol (1:1). Aliquots were analyzed for cholesterol according to the procedures of Sperry and Brand.[4] Aliquots of the alcohol-acetone extract were evaporated to dryness, extracted with petroleum ether and the total lipide carbon was determined by the manometric technic of Van Slyke and Folch.[5] Total nitrogen was determined by the micro-Kjeldahl procedure.

RESULTS

Electrophoresis. The percentage distributions of the protein components of plasmas and four fractions (I, II + III, IV-4 and V) together with typical ascending patterns are shown in Figures 1 and 2. Fraction IV-1 is omitted due to insufficient amounts for analyses. The variations in distribution of the various components are generally greater in the fractions than in whole plasma. The

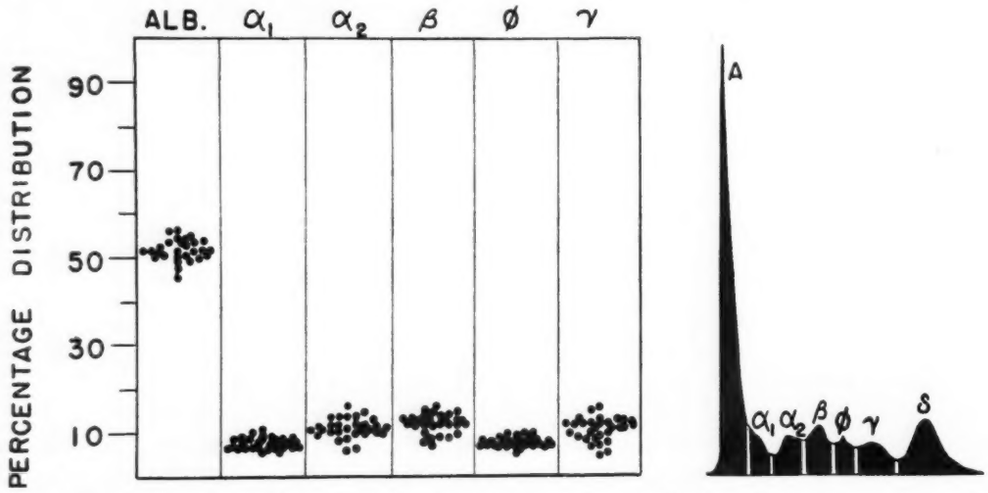

FIG. 1. Electrophoretic analyses of whole plasma; percentage distribution of protein components in plasma.

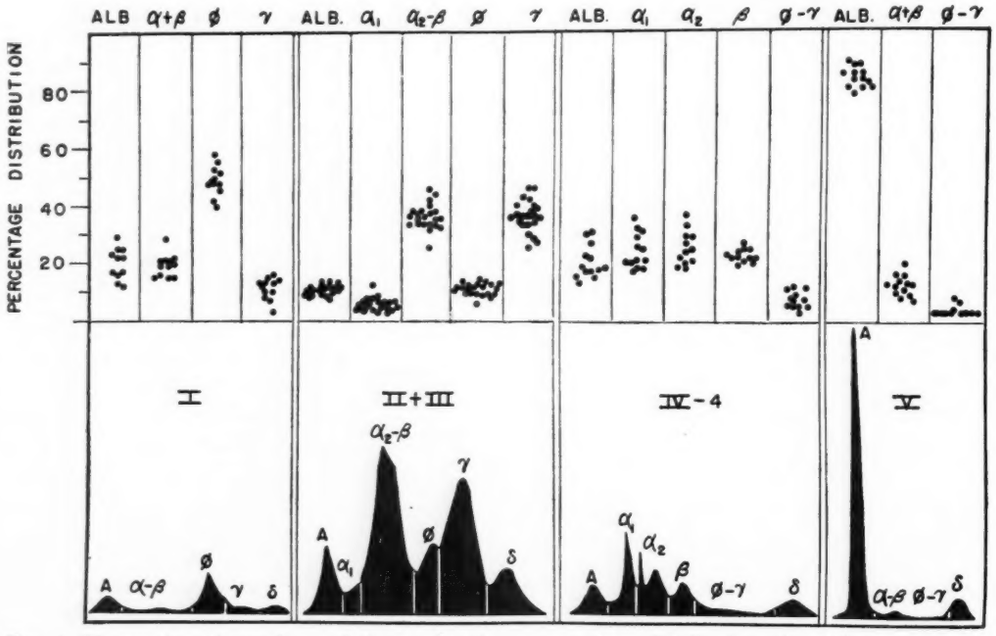

FIG. 2. Electrophoretic analyses of plasma fractions; percentage distribution of protein components in Fractions I, II + III, IV–4 and V.

mean values for percentage distribution of the protein components of the plasma and its fractions (Table I) are similar to those presented by the Harvard investigators.[1,2] The small differences noted may be due to incomplete resolution in the microcell, age of the plasma at the time of fractionation, sampling of individuals instead of pooled plasmas and slight differences in fractionation technic.

The mobilities of each component were determined for each fraction but were too variable for identifying the respective proteins. The relative positions of the components in the electrophoretic pattern were used as the means of identification.

TABLE I
MEAN PERCENTAGE AREA DISTRIBUTIONS OF ELECTROPHORETIC PATTERNS OF PLASMA AND FOUR FRACTIONS

Electrophoretic Component	Whole Plasma (30)* %	Fractions I (12) %	II + III (22) %	IV-4 (13) %	V (13) %
Albumin	52	20	10	21	84
α_1	8	..	5	24	
α_2	11	19	36	26	13
β	12	..	..	23	
ϕ	7	49	13	6	4
γ	11	12	36		

* Figures in parentheses represent number of samples. All the fractions in twelve individual subjects were analyzed.

TABLE II
MEAN VALUES IN MG. OF THE CONTENTS OF PROTEIN NITROGEN, LIPIDE CARBON AND CHOLESTEROL IN EACH FRACTION PER 100 ML. PLASMA

Plasma	I	II + III	IV-1	IV-4	V	Total Contents in Fractions, %
Protein Nitrogen (30)*						
1083	87	258	40	124	477	986 (91)†
Total Lipide Carbon (30)						
491	44	254	48	74	42	462 (94)
Cholesterol (30)						
180	13‡	118	5‡	23‡	7‡	166 (92)
% Free Cholesterol						
26		29				

* Number of samples analyzed.
† Percentage recovery in fractions.
‡ Represents a limited number of determinations.

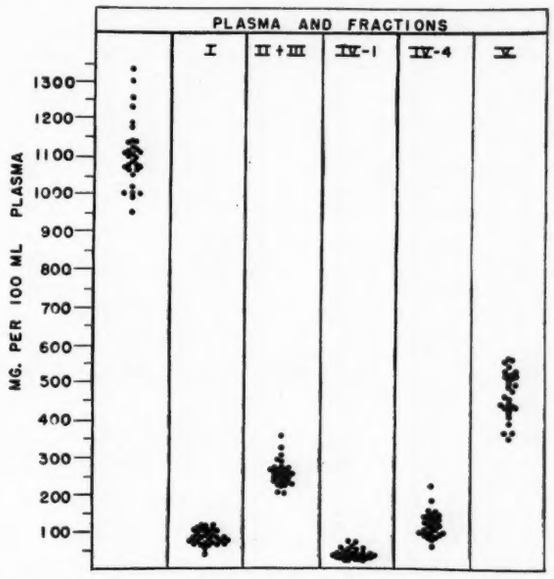

FIG. 3. Protein nitrogen contents of plasma and five plasma fractions.

Distribution of the nitrogen in plasma and five fractions of thirty subjects is shown in Figure 3. The greatest variations in individual values are seen in whole plasma and in Fraction V. The mean values for each fraction are shown in Table II. Approximately 75 per cent of the plasma protein is present in Fractions II + III and V. The distribution of the fractions in terms of nitrogen is similar to that noted by Cohn et al.[1]

The lipide carbon values are shown graphically in Figure 4 and the mean values are given in Table II. More than one-half of the lipide carbon is present in Fraction II + III. According to the mean values there is an excellent recovery of lipide in the five fractions. However, an analysis of individual plasmas shows wide differences in the percentage recovery, varying from 75 to 118 per cent. The indi-

vidual lipide carbon contents of Fraction II + III constitute between 43 and 70 per cent of the total content of the plasma.

Detailed and mean data for cholesterol are presented in Figure 5 and Table II. Approximately 70 per cent of the total cholesterol of the plasma is present in Fraction II + III. The marked constancy of the percentage of free cholesterol of Fraction II + III is worthy of note. The free cholesterol in the remaining fractions could not be determined accurately due to the small amounts present.

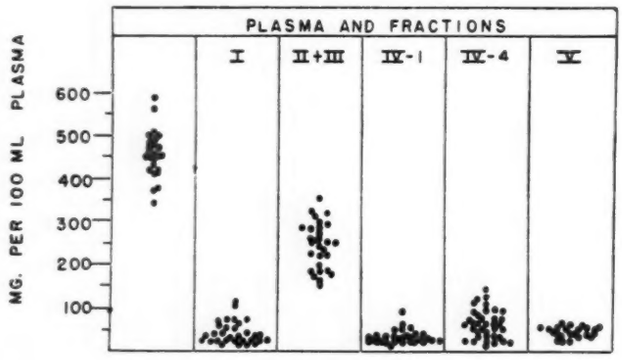

FIG. 4.

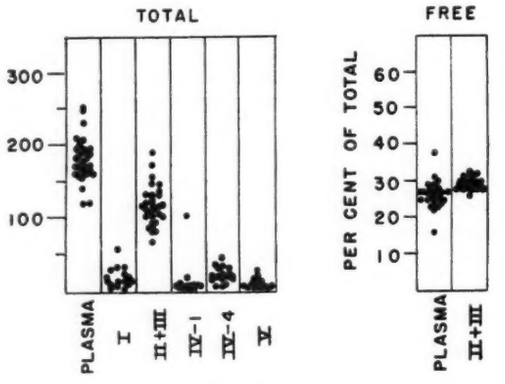

FIG. 5.

FIG. 4. Lipide carbon contents of plasma and five fractions.
FIG. 5. Total cholesterol of plasma and five plasma fractions; and percentage free cholesterol in plasma and Fraction II + III.

COMMENTS

According to Cohen and Thompson,[6] the area distributions and mobilities of patterns obtained with the micro- and macrocells are in good agreement with each other. The microcell is essential in the present investigation because of the small amounts of available material. Fairly good agreement for the patterns obtained by the two types of cells has also been found in this laboratory. However, the mobility data are unsatisfactory due to the large variations for any given component. It is difficult to resolve satisfactorily the complexes in the ϕ and γ areas of Fractions IV-4 and V and in the α-β area of Fractions I and II + III.

SUMMARY

Methods are described for fractionating comparatively small volumes of plasma obtainable from individual subjects, by the low temperature-ethanol procedures developed by E. J. Cohn and associates for large scale fractionation of pooled plasmas.

Electrophoretic, nitrogen and lipide analyses of the plasma and five fractions (I, II + III, IV-1, IV-4 and V) of healthy young men are presented.

Acknowledgments: The authors are indebted to Dr. Stephan Ludewig, Dr. E. C. Gjessing, Mr. J. P. Lewis, Mr. E. R. Berry and Miss B. A. Lentz for advice and technical assistance.

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II. Electrophoretic, Nitrogen and Lipide Analyses of Plasma and Plasma Fractions in Disease*

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Changes in the distribution and properties of the plasma proteins noted during disease are of considerable interest to clinicians and investigators. In a recent review of the literature dealing with plasma proteins in disease Gutman[1] pointed out that distribution of these proteins is generally not specific for any one disease but is characterized by a decrease in albumin and an increase in various globulin components.

Most of the available information is based on electrophoretic studies of plasma and plasma fractions obtained with neutral salt precipitation. The inability to correlate the changes in plasma proteins with a specific disease detracts from the diagnostic value of plasma protein fractionation by present salting-out methods. The carefully controlled fractionation procedures of Cohn and associates[2] provide another approach to the study of this problem. Application of these technics to relatively small volumes of dog,[3] rat[4] and goat[5] plasmas reveal changes in the distribution of protein components after injury.

In a previous paper[6] the plasma proteins of normal young men were fractionated by the low temperature-ethanol procedures and standards were established for the electrophoretic, nitrogen and lipide distributions of the plasma fractions. In this investigation these same procedures were applied to the plasmas of patients with a variety of diseases.

Results

The plasmas and the plasma fractions of patients with multiple myeloma, hepatic disease, nephrotic syndrome, malignant hypertension, pneumonia and a variety of other diseases were studied.

Multiple Myeloma. The data in six cases of proven multiple myeloma are presented. Two of these patients had normal plasma nitrogen concentrations but hyperglobulinemia was present in all cases. (Fig. 1.) Most of the nitrogen values in Fractions I and II + III were elevated while the albumin contents (Fractions V) were all decreased. The protein contents of Fractions IV-1 and IV-4 were not affected. The lipide carbon contents of the plasma and Fraction II + III were decreased except in one instance; the values for the remaining fractions were normal. (Fig. 1.) The total cholesterol contents were somewhat decreased and the percentage-free cholesterol was not appreciably affected.

The electrophoretic patterns for the plasma and four fractions of Patient O. H. are shown in Figure 2; pertinent patterns are shown for the remaining five patients. (Fig. 3.) The abnormal protein component ("M") has the mobility of gamma globulin in five of the six patients and has the solubility characteristics of gamma globulin in the fractionation procedure. It is the chief protein in Fraction II + III.

The electrophoretic analysis of the protein components of the plasma and Fraction

* From the Biochemical Laboratory, University of Virginia Medical School, Charlottesville, Va. This work was made possible by a grant from the Office of Naval Research.

II + III of all patients are graphically presented in Figure 4. It will be noted that the gamma globulin component was increased in five patients; two determinations taken at an interval of one month for Patient C. H. were elevated in the fibrinogen range in both the plasma and Fraction II + III. The α_2-β area was decreased in Fraction II + III in all cases. Distribution of the components of Fraction IV-4 and V of multiple myeloma plasmas was normal.

The distribution and properties of component M were not uniform. In patient O. H. (Fig. 2) most of the abnormal protein was present in Fraction II + III, but an appreciable amount was also present in Fraction I. Although the mobility of the abnormal protein of the plasma of G. H.

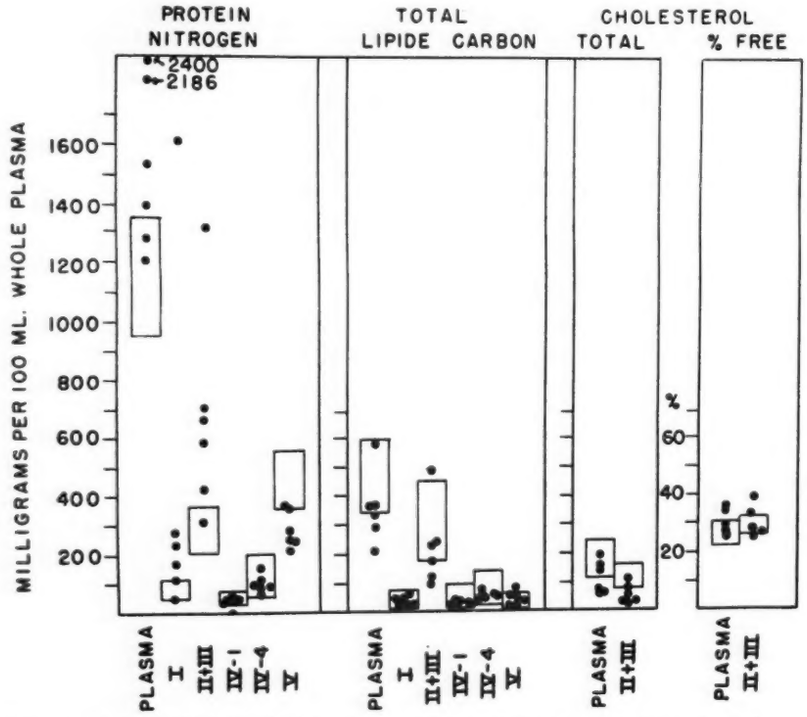


FIG. 1. Protein nitrogen, lipide carbon and cholesterol contents in the blood plasma and fractions of six cases of multiple myeloma. The rectangles in this and other figures represent the limit of variations in normal subjects.

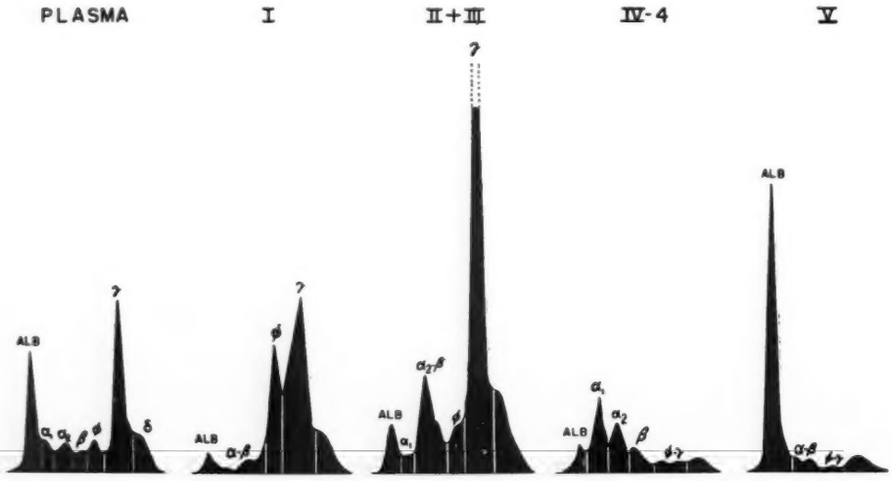


FIG. 2. Electrophoretic patterns of plasma and four fractions of a case of multiple myeloma; patient O. H.

(Fig. 3) was in the γ range, 72 per cent of the total plasma nitrogen (2.4 gr. per cent) was present in Fraction I; a saline solution of this fraction solidified on standing. It was from this patient was unusually viscous; this property was not observed after the patient was treated with stilbamidine for a month. A viscous protein was also described

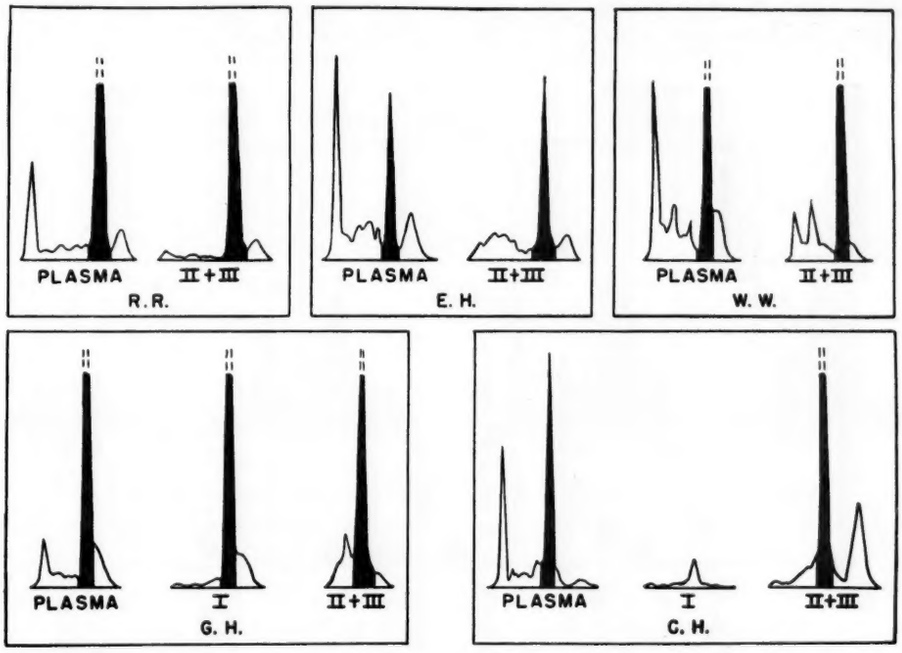


FIG. 3. Electrophoretic patterns of the plasma and Fractions I and II + III of five cases of multiple myeloma. The solid portion of the pattern represents the "M" component.

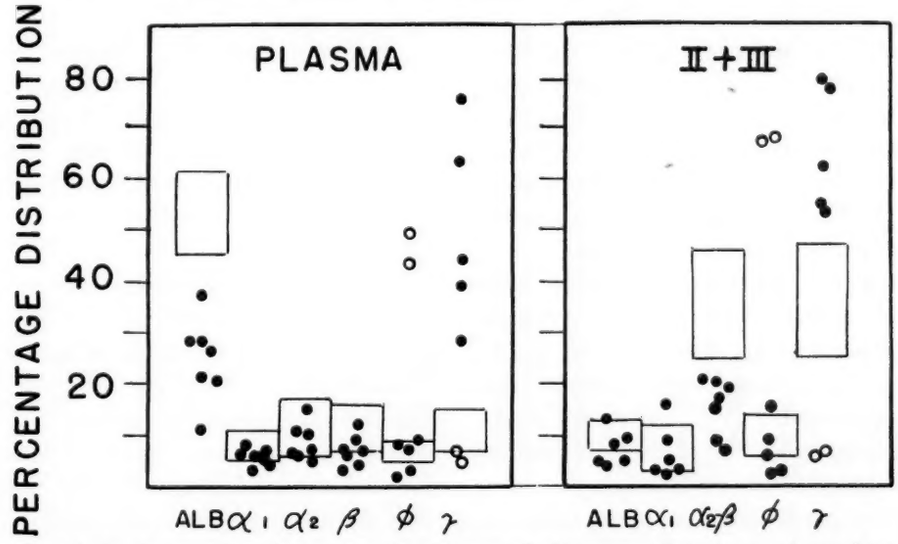


FIG. 4. Analyses of the electrophoretic patterns of plasma and Fraction II + III of six cases of multiple myeloma. The open circles designate the results obtained for patient C. H.

noted that the M component of the plasma of C. H. (Fig. 3) appeared to have the mobility of fibrinogen but on fractionation was absent in Fraction I. A solution of Fraction II + III of the first plasma obtained by Shapiro et al.[7] It is improbable that this therapy was responsible for the change in physical property.

Liver Disease. In this group five cases of hepatitis of virus etiology and five of

Laennec cirrhosis are discussed. The results are shown in Figures 5 and 6.

Despite the normal values for plasma nitrogen (Fig. 5) these patients exhibit hyperglobulinemia as evidenced by the elevated values in Fractions I and II + III distribution of the components of the electrophoretic patterns tended to return to the normal ranges. No demonstrable differences in the electrophoretic patterns were seen at widely varying intervals in two of the cirrhotics studied.

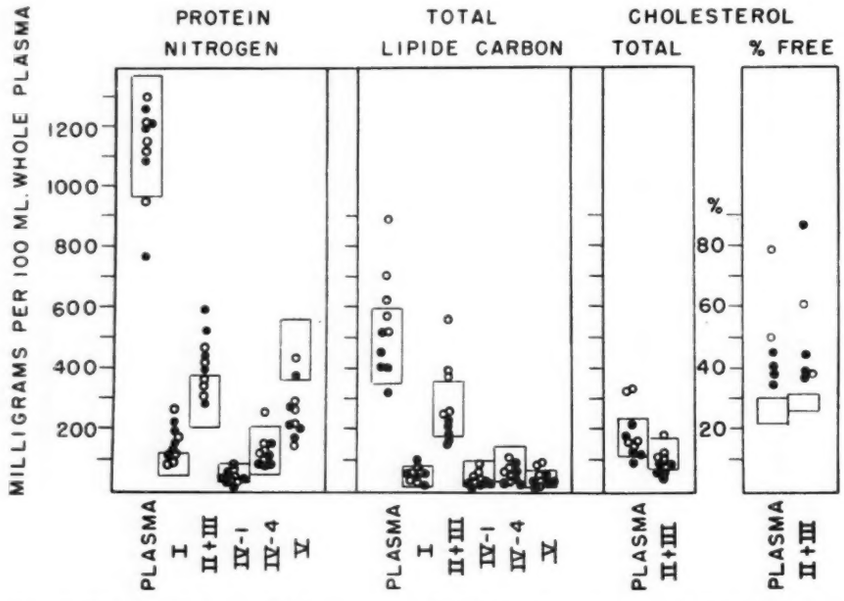


FIG. 5. Protein nitrogen, lipide carbon and cholesterol contents in the blood plasma and fractions of ten cases of liver disease; ○ = hepatitis; ● = cirrhosis.

and decreases in albumin (Fraction V). The lipide carbon contents are not appreciably affected. The total cholesterols of Fraction II + III of the cirrhotics are below normal. Liver damage is reflected in the increased values for the percentage-free cholesterol, particularly in the hepatitis patients.

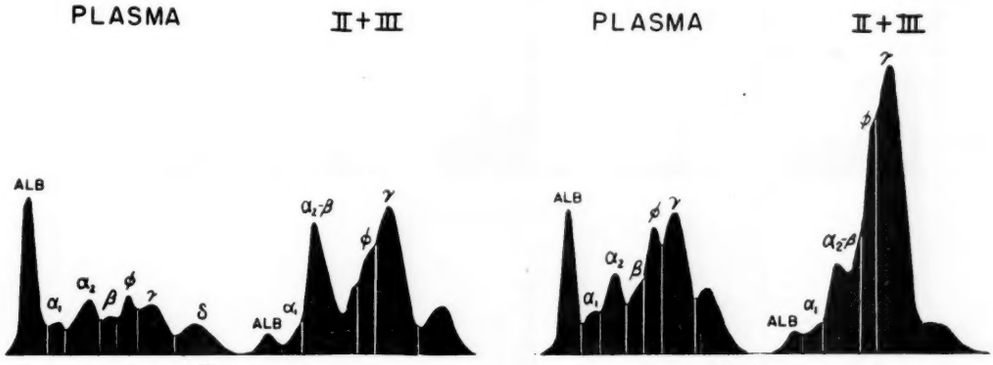
Electrophoretic patterns of plasma and Fraction II + III from two cirrhotic patients in the terminal stage are shown in Figure 6. The distribution and concentration of the protein components are quite different under conditions which are clinically identical. Most of the patients with cirrhosis have electrophoretic patterns similar to Case II. The electrophoretic patterns of hepatitis plasma and Fraction II + III are qualitatively similar to those of cirrhosis; the γ globulin area tends to be smaller in the hepatitis patients.

In one patient with hepatitis who showed clinical improvement the lipide and nitrogen contents of the plasma and fractions and

Nephrotic Syndrome. Studies on five patients with marked albuminuria, edema, hypo-albuminemia and hypercholesterolemia are presented. In two cases patients were studied at intervals during treatment. The data are summarized in Figures 7 and 8.

The very low nitrogen content of Fraction V and marked elevation of lipide carbon and cholesterol contents of the plasma and Fraction II + III are the outstanding chemical changes noted in Figure 7. Two plasma nitrogen concentrations of a patient treated for a long period are in the control range but the albumin contents remain subnormal. Electrophoretic patterns of the plasma and the fractions of two patients are shown in Figure 8. The changes seen in the plasma of subject V. A., a twelve year old girl with a typical nephrotic syndrome, were similar to those described by other investigators. The α_2-β components of Fractions II + III and V were increased and the

albumin component of Fraction v was markedly decreased. The nephrotic syndrome of patient S. P., a forty-five year old male, was complicated by psoriasis and atrophic arthritis. In this case the α_2 component was prominent in all patterns except Fraction i; the fibrinogen was increased in the plasma and Fractions i and ii + iii; the β component was present in small amounts.



Patient 1 Patient 2

FIG. 6. Electrophoretic patterns of two cirrhotic patients in the terminal stage.

The electrophoretic analyses of the plasmas of all patients showed a marked decrease of albumin and an elevation of the α_2, β and ϕ components. The α_2-β areas of Fraction ii + iii were consistently increased.

Malignant Hypertension. The results obtained in four patients in various phases of this disease are given. (Fig. 9.) The outstanding changes in the chemical analyses were as follows: increases in the nitrogen contents of Fraction i and ii + iii and decreases in Fraction v; decreases of total cholesterol of Fraction ii + iii in three of the four patients and elevation in the percentage-free cholesterol of the plasma and Fraction ii + iii. No striking change was observed in the electrophoretic analyses except for a decrease in the albumin component of the plasma.

Pneumonia. The patients in this group represent two severely ill patients due to type 33 pneumococcus (J. W.) and tularemia (H. D.) and three moderately severe pneumonias of unknown etiology (C. M., A. P. and M. G.).

Case i (J. W.) ran a particularly stormy course with continuous high fever during the first two weeks. The plasma and Fraction ii + iii pattern (Fig. 10) on the ninth day after the onset of illness was unusual due to the marked increases in the α globulins and fibrinogen. On the sixteenth day the patient showed definite signs of improvement. The patient was discharged on the twenty-third day and was back at work on the forty-third day but the electrophoretic patterns, pulmonary x-ray and physical findings at this time had not yet returned to normal. During recovery the electrophoretic patterns were characterized by increases in the γ globulins and albumin and decreases in α globulin and fibrinogen.

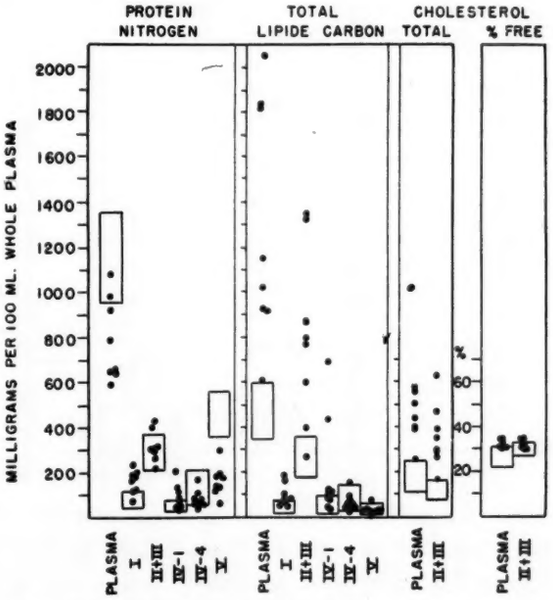


FIG. 7. Protein nitrogen, lipide carbon and cholesterol contents in the blood plasma and fractions of five cases with the nephrotic syndrome.

The changes in the nitrogen distribution in Case I are noteworthy since the albumin content decreased and the γ globulin-rich Fraction II + III increased at about the time of clinical improvement. (Table I.) After this time values for the various fractions tended to return to normal. The changes in the lipide carbon were not striking or consistent. The cholesterol contents, however, changed from subnormal to normal values, with recovery.

The tularemic pneumonia patient (H. D.) was very ill when admitted to the hospital on the ninth day of his illness. At this time the nitrogen contents of the plasma and its fractions, particularly Fraction V, were decreased; the cholesterol contents were subnormal and the percentage-free cho-

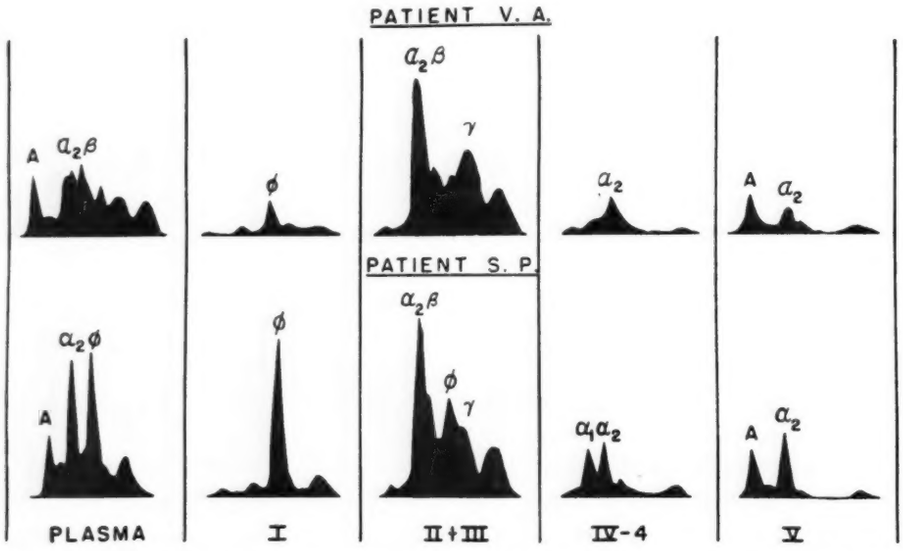


FIG. 8. Electrophoretic patterns of the plasma and four fractions of two cases with the nephrotic syndrome.

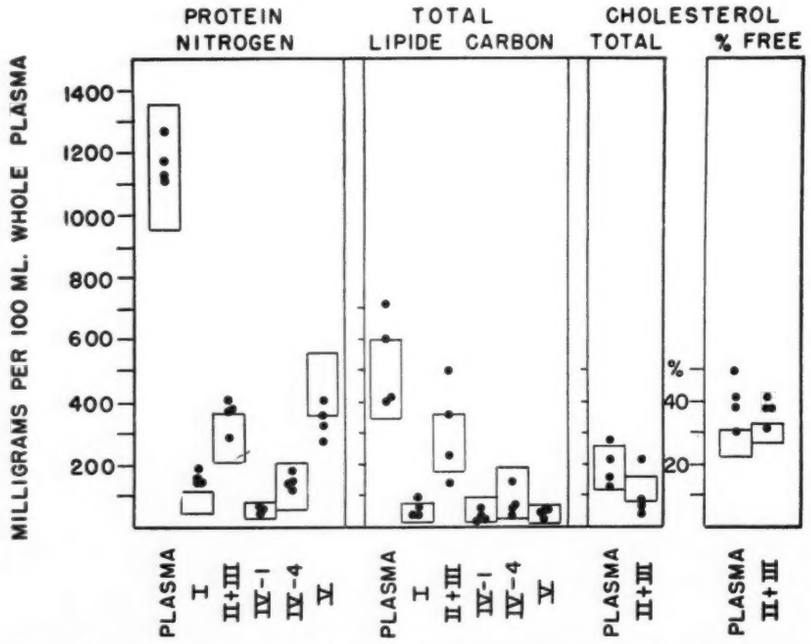


FIG. 9. Protein nitrogen, lipide carbon and cholesterol contents in the blood plasma and fractions of four cases of malignant hypertension.

lesterol was elevated in the plasma and Fraction II + III. (Table I.) At the time of definite improvement (the twenty-eighth day) the nitrogen content of the plasma was in the normal range due chiefly to increases in the fibrinogen, γ globulin and albumin patterns of the plasma and fractions were not particularly striking in these three patients.

Miscellaneous Diseases. The following diseases were studied: lymphopathia venereum; heart failure (six cases); acute

TABLE I

NITROGEN, LIPIDE CARBON AND CHOLESTEROL CONTENTS PER 100 ML. OF PLASMA AND PLASMA FRACTIONS IN FIVE CASES OF PNEUMONIA AT VARYING INTERVALS DURING THE ILLNESS

Day of Illness	Protein Nitrogen						Total Lipide Carbon						Cholesterol	
	Plasma	I	II + III	IV-1	IV-4	V	Plasma	I	II + III	IV-1	IV-4	V	Plasma	II + III
Case I, J. W., a male, aged 31														
9	903	175	212	22	152	200	378	82	139	21	41	41	81	41
16	1260	193	526	22	302	119	229	94	109	22	80	47	98	37
23	1330	221	516	30	199	279	394	128	128	42	134	43	139	34
43	1232	133	403	58	129	460	432	95	164	29	98	71	158	69
Case II, H. D., a male, aged 27														
10	725	64	216	33	70	252	474	38	326	40	53	34	89 (57)*	68 (63)*
17	808	75	293	26	99	244	418	36	290	19	50	23	107 (49)	87 (42)
28	1350	179	518	18	117	334	470	38	249	17	78	44	208 (35)	136 (34)
Case III, C. M., a male, aged 44														
5	974	223	200	87	179	274	523	33	169	38	63	41	72 (46)	49 (40)
7	966	160	237	55	161	308	453	36	174	48	35	36	95 (31)	67 (36)
Case IV, A. P., a male, aged 29														
5	974	144	284	45	143	296	389	42	218	40	51	18	79 (40)	58 (44)
12	1192	207	403	50	86	334	467	60	219	35	35	29	116 (30)	91 (29)
Case V, M. G., a female, aged 19														
7	897	150	281	34	91	281	366	79	154	28	89	37	102 (38)	44 (34)
14	1040	120	360	26	108	318	543	183	303	59	50	54	168 (33)	135 (30)

* Figures in parentheses represent the percentage-free cholesterol.

in Fractions I, II + III and V, respectively. The lipide carbon contents were not appreciably affected during the illness. The cholesterol contents rose and the percentage-free cholesterol decreased to normal limits.

In the three remaining patients with pneumonia the pertinent chemical changes (Table I) during recovery were similar in general to those observed in patients J. W. and H. D. The changes in electrophoretic

nephritis; pernicious anemia; sickle cell anemia; periarteritis nodosa; arsenic poisoning; early syphilis before and after treatment (two cases); Hodgkin's disease before and after treatment with nitrogen mustards (three cases) and rheumatic fever (two cases). The electrophoretic patterns of the plasma in these patients were similar to those obtained by other investigators. The patterns of Fraction II + III usually reflect

the outstanding changes in the globulin components of the plasma. Generally there is an increase in the nitrogen content of Fraction II + III and a decrease of Fraction V. No characteristic changes in the lipide values were observed.

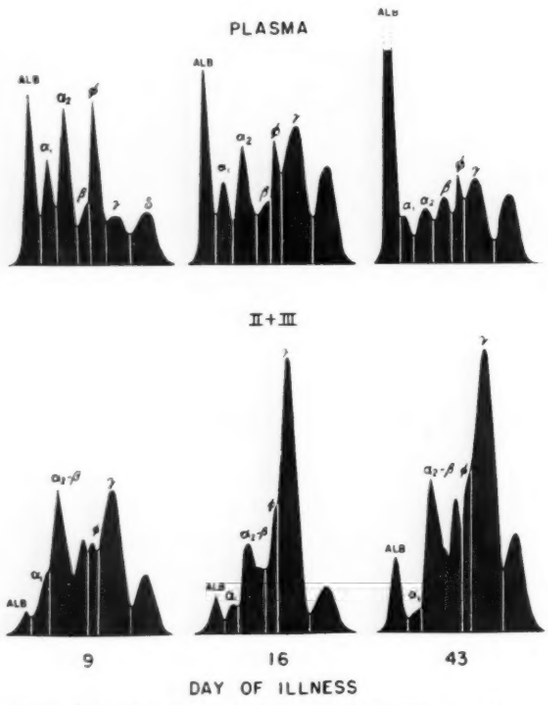


FIG. 10. Electrophoretic patterns of plasma and Fraction II + III of a case of pneumococcic pneumonia at varying intervals during the disease; patient 1.

COMMENTS

The literature concerned with the electrophoresis of plasma in disease was reviewed by Stern and Reiner,[8] Luetscher[9] and Gutman.[1] It is generally agreed that this procedure is of limited value as a diagnostic test. Corroborative evidence is presented in this paper which shows a lack of specificity of the electrophoretic pattern of plasma in most diseases.

The nitrogen, lipide carbon and cholesterol contents of each of the five plasma fractions could be determined in relatively small volumes of plasma. In most diseases the nitrogen content of the fibrinogen-rich Fraction I is elevated due chiefly to an increase in fibrinogen. The protein content of Fraction II + III is usually increased except in nephrotic cases. The nitrogen of the albumin-rich Fraction V is depressed in all diseases of moderate or marked severity and this is particularly striking in nephrosis and liver disorders. The increased lipide carbon contents of the plasmas of patients with nephrosis and hepatitis are usually reflected in Fraction II + III. It is striking that the ratio between the cholesterol contents of total plasma and Fraction II + III remains within the normal range[6] in the diseases studied. The values for the percentage-free cholesterol are approximately the same for plasma and Fraction II + III.

Electrophoretic analyses of the plasma fractions yield more detailed information concerning the distribution of proteins than is observed in the plasma. Fraction II + III usually shows the greatest qualitative changes in disease due to variations in the distribution of the α^2-β and γ globulins. The remaining fractions do not show appreciable variations in the percentage distribution of the components. At present it is impossible to assess the significance of the percentage distribution of the components in these fractions. Increases in a given component may indicate the presence of an abnormal protein or an increased content of the normally-occurring protein. In order to appreciate the changes seen in plasma fractions it will be necessary to separate these components and determine their physical and chemical characteristics. Such studies would be particularly applicable to plasmas of patients with the nephrotic syndrome, liver diseases, multiple myeloma and severe infections.

SUMMARY AND CONCLUSIONS

The plasmas of patients with multiple myeloma, liver disease, nephrotic syndrome, malignant hypertension, pneumonia and a variety of other diseases were separated quantitatively into five fractions (I, II + III, IV-1, IV-4 and V) by the ethanol-low temperature, low salt procedures. These plasma and fractions were analyzed electrophoretically and their nitrogen, lipide carbon and cholesterol contents were determined.

The abnormal protein component (M)

of multiple myeloma plasma is usually present in Fraction II + III but may also be found in Fraction I. The mobility characteristics of this protein in plasma do not necessarily determine the fraction in which the M component is present.

The degree of alteration in the plasma protein patterns is, in general, determined by the severity of the disease. The abnormalities in the distribution of the protein components noted, particularly in Fraction II + III, appear to be non-specific. Significant changes in the nitrogen and lipide distributions may be seen in Fractions I, II + III or V.

Acknowledgments: The authors are indebted to Mr. J. P. Lewis, Mr. E. R. Berry, Miss B. A. Lentz and Miss F. L. Jones for technical assistance.

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A Spontaneously Precipitable Protein in Human Sera, with Particular Reference to the Diagnosis of Polyarteritis Nodosa*

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DURING routine analysis of sera in the chemistry laboratory one of us (F. W.) noted a precipitate in a certain serum after cooling for twenty-four hours at 4°C. On repeated examination of the same serum under similar conditions the same result was obtained. The clinical diagnosis in this case (Case I) was polyarteritis nodosa, subsequently proved by postmortem examination. All sera analyzed in the laboratory thereafter were examined for this precipitate. A second case (Case II) was subsequently found showing the same type of precipitate. The clinical diagnosis here again was polyarteritis nodosa, also proved by postmortem examination.

On further analyses of sera three additional cases were found in which the clinical diagnoses were portal cirrhosis of the liver (Case III), subacute bacterial endocarditis (Case IV) and septicemia (Case V). The patient with portal cirrhosis died but permission for postmortem examination was not obtained. The remaining two patients have been under follow-up observation. A sixth case was observed recently in which the clinical diagnosis was polyarteritis nodosa, proved by biopsy. A detailed study of the serum of this last patient was undertaken in order to determine the nature of the precipitate by means of electrophoretic analysis.

CASE REPORTS

CASE I. F. C., a fifty-four year old white male, was admitted to Lincoln Hospital in a semicomatose condition on January 17, 1947. The diagnosis of polyarteritis nodosa was made because of the presence of fever, leukocytosis, changes in the ocular fundus, hematuria, azotemia, anuria, peripheral neuritis, purpura, gangrene and convulsive seizures. No eosinophilia was detected. Serum total proteins rose from 4.6 Gm. per cent (albumin/globulin ratio of 2.4/2.2) to 6.8 Gm. per cent (albumin/globulin ratio of 3.6/3.2) and 7.1 Gm. per cent (albumin/globulin ratio of 4.1/3.0), with the cephalin flocculation at first negative, then plus-minus and then 3 plus before death on April 7, 1947, the eighty-eighth hospital day. Blood non-protein nitrogen reached 114 mg. per cent. Postmortem examination confirmed the clinical diagnosis. Lesions of polyarteritis nodosa were found in the kidneys, pancreas, heart, lungs, skin, muscles, seminal vesicles, mediastinal vessels and liver.

This was the first case in which the presence of a spontaneously precipitable protein was noted.

CASE II. M. L., a thirty-six year old Negro male, was first admitted to Lincoln Hospital on May 25, 1945, because of migrating joint pains of three days' duration. Findings suggested the diagnosis of acute rheumatic fever with polyarthritis. Response to salicylate therapy was so good that the patient left the hospital against advice after twenty days.

The second admission was on June 6, 1947, because of weakness, fever and pain in the right wrist. A diagnosis of acute exacerbation of rheumatic polyarthritis was proposed and the patient was again given salicylates. Shortly afterward hypertension, proteinuria and hematuria appeared. On July 2, 1947, after the onset

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of spiking temperature and generalized edema, polyarteritis nodosa was first suspected. It was at this time that the laboratory demonstrated the appearance of a spontaneously precipitable protein in a specimen of venous blood withdrawn for analysis. Biopsy of gastrocnemius muscle was negative for evidence of polyarteritis nodosa. There was no eosinophilia.

Total serum protein was 5.3 Gm. per cent, with albumin/globulin ratio of 2.9/2.4; cephalin flocculation was negative. Later the total protein was 5.6 Gm. per cent, with albumin/globulin ratio of 3.1/2.5; the cephalin flocculation was plus-minus. Blood non-protein nitrogen was 112 and 132 mg. per cent. A second biopsy of gastrocnemius, July 17, 1947, showed hyalinized blood vessels.

In spite of the development of a wrist drop and other evidence of peripheral neuritis, as well as of pericarditis, the patient left the hospital against advice on July 29, 1947. Postmortem confirmation of polyarteritis nodosa was made fortuitously because an assistant medical examiner had to be called when the patient died at home ten days later unattended by a physician. The findings of the assistant medical examiner indicated the presence of polyarteritis nodosa of the intestine, kidneys, lungs and testicles, with bilateral hydrothorax, pericarditis and ascites.

In this case there was a history of taking sulfonamides for scarlet fever four weeks before the first admission. A spontaneously precipitable protein appeared before biopsy confirmation. It appeared in the absence of eosinophilia. Azotemia was present and the cephalin flocculation was becoming increasingly positive. The first diagnosis of polyarteritis nodosa was made less than one month after the second admission.

Case III. E. O., a forty-two year old white alcoholic female, admitted to Lincoln Hospital in a semicoma on March 8, 1947, presented the typical picture of cirrhosis of the liver. Total protein was 6.4 Gm. per cent. Later examinations showed total protein 6.0 Gm. per cent, with albumin/globulin ratio of 2.9/3.1 and total protein 6.1 Gm. per cent, with albumin/globulin ratio of 2.9/3.2. Cephalin flocculation was 4 plus. Blood urea nitrogen was 67 and 69 mg. per cent, with a non-protein nitrogen of 132 and 102 mg. per cent. The patient was given penicillin for right lower lobe pneumonia. She developed bilateral wrist drop and signs of peripheral neuritis in spite of massive vitamin therapy and she died suddenly after the onset of extreme dyspnea on April 5, 1947. Postmortem examination was not permitted.

In this case a spontaneously precipitable protein was present when there was a reversal of the albumin/globulin ratio, 4 plus cephalin flocculation and azotemia.

Case IV. H. P., a white female, was twenty-six years old when she was first admitted to Lincoln Hospital as an obstetric patient on March 31, 1940. She was also treated with sulfonamides for acute pyelitis and acute mastitis in June, 1940, and in July, 1940 for an ischiorectal abscess. In May, 1947, aged thirty-three, she was admitted for spontaneous subarachnoid hemorrhage. The presence of a palpable spleen, a systolic murmur and clubbing of the fingers, even in the absence of petechiae and of positive blood culture, suggested subacute bacterial endocarditis. Laboratory studies included: total protein 7.9 Gm. per cent, with an albumin/globulin ratio of 3.5/4.4; total protein 6.9 Gm. per cent, with an albumin/globulin ratio of 3.5/3.4; total protein 6.9 with an albumin/globulin ratio of 3.4/3.5. Cephalin flocculation tests were 3 plus and 4 plus. She left against advice after five weeks. She continued to run low grade fever at home in spite of daily injections of penicillin in oil and beeswax given by her private physician.

She re-entered the hospital on August 14, 1947, because of continuous headache, sleeplessness and fleeting dull aches in the leg muscles, together with paresthesias. Biopsy of skin and of gastrocnemius muscle was negative for polyarteritis nodosa. Enlarged heart, splenomegaly, systolic murmur and clubbing were still present. Diagnosis of subacute bacterial endocarditis was confirmed by the finding of three successive blood cultures positive for Streptococcus viridans one week after admission. She received appropriate treatment with penicillin and developed petechiae in the course of therapy. On August 27, 1947, a spontaneously precipitable protein was noted in a specimen of blood taken for analysis. Total protein was 6.6 Gm. per cent, with albumin/globulin ratio of 3.8/2.8. After removal of the precipitate the same specimen showed a total protein of 6.6 Gm.

per cent, with albumin/globulin ratio of 3.0/3.6. Cephalin flocculation at this time was 4 plus. On a later specimen total protein was 7.3 Gm. per cent and the albumin/globulin ratio was 3.6/3.7, with 4 plus cephalin flocculation. The clinical diagnosis was congenital heart disease, probably interventricular septum defect, in conjunction with subacute bacterial endocarditis. Total penicillin administered in the forty-one days from August 23, 1947, to October 3, 1947, when she left against advice, was 82 million units.

On re-admission from October 5 to October 17, 1947, for weakness, headaches, paresthesias and unconsciousness, she received an additional 26 million units of penicillin. Angiocardiography performed at another hospital later that month confirmed the clinical diagnosis of interventricular septum defect. She is being treated at home by a staff member, through whose cooperation follow-up examinations and blood studies have been made possible. The clinical condition is good and apparently the subacute bacterial endocarditis has been cured. A spontaneously precipitable protein is present in some examinations and absent in others.

In this patient a spontaneously precipitable protein appeared when the total protein was relatively high, when the albumin/globulin ratio was reversed and when 4 plus cephalin flocculation was present.

Case v. W. W., a fifty-eight year old Negro male, was admitted to Lincoln Hospital on January 12, 1947, acutely ill with bronchopneumonia and rheumatoid arthritis. Eosinophilia of 15 per cent and the finding of a tarry stool two days later led to suspicion of polyarteritis nodosa, made stronger by the appearance later that day of a urea frost and a blood non-protein nitrogen of 198 mg. per cent. Muscle biopsy, however, was negative. Acidotic breathing, massive edema and ascites also appeared. Total protein was 5.4 Gm. per cent, with albumin/globulin ratio of 2.9/2.5. Later examinations showed total protein 7.4 Gm. per cent, with albumin/globulin ratio of 3.1/4.3 and 3 plus cephalin flocculation; total protein 8.4 Gm. per cent, with albumin/globulin ratio 4.2/4.2 and plus-minus cephalin flocculation; total protein 8.0 Gm. per cent, with albumin/globulin ratio of 3.9/4.1 and plus-minus cephalin flocculation and total protein 8.0 Gm. per cent, with albumin/globulin ratio 3.9/4.1 and plus-minus cephalin flocculation. A spontaneously precipitable protein appeared during this time. After a stormy course penicillin therapy resulted in recovery and the patient left against advice on the sixtieth hospital day. Because the blood culture of February 18, 1947, was positive, final diagnosis was septicemia caused by hemolytic streptococcus. Since only one positive blood culture was obtained, the staff was not satisfied with the diagnosis and chose to consider the case as possible polyarteritis nodosa. The patient returned for follow-up study several times and a small amount of spontaneously precipitable protein was found. He refused another muscle biopsy when last seen, about nine months ago.

In this case a spontaneously precipitable protein appeared with the elevation of the total protein and the reversal of the albumin/globulin ratio, even in the absence of strongly positive cephalin flocculation. Azotemia was also present.

Case vi. J. S., a sixty-four year old white male, was admitted on March 9, 1948, because of pains in the legs and a burning sensation in the soles of his feet present for five weeks, causing such discomfort that he could not rest day or night. He had been treated in two other hospitals since 1941 for a duodenal ulcer, gallbladder disease and myocardial infarction. Extensive investigation in 1943 showed a duodenal ulcer with marked deformity of the duodenal bulb and crater of the posterior wall. In May, 1946 the duodenal ulcer perforated and surgical repair was performed. In July, 1947 and September, 1947 he was treated for bleeding ulcer. Blood pressures were 170/110, 190/110 and 170/100. Urinalyses varied from a trace of albumin to 3 plus albumin, with occasional casts, white blood cells and red blood cells. Some arteriovenous nicking and diminution in the caliber of the fundal arterioles were noted.

On admission to Lincoln Hospital, March 9, 1948, he looked acutely ill, with a temperature of 101.4°F. and a blood pressure of 160/90. Urinalysis was negative. Electrocardiogram showed evidence of coronary insufficiency. When a spontaneously precipitable protein appeared in the first blood specimen withdrawn

for analysis, the diagnosis of polyarteritis nodosa was suggested. Clinical findings of hypertension, low grade fever and bizarre complaints, with the symptoms of peripheral neuritis, completed the picture.

On March 15, 1948, total protein before refrigeration of the blood specimen was 5.8 Gm. per cent, with an albumin/globulin ratio of 2.9/2.9. After refrigeration and removal of the precipitate total protein was 5.5 Gm. per cent, with albumin/globulin ratio of 2.7/2.8. Cephalin flocculation was 4 plus. Blood urea nitrogen was 46 mg. per cent and non-protein nitrogen was 85 mg. per cent. No eosinophilia was noted. Biopsy from the right deltoid region on March 22, 1948, showed fresh lesions of polyarteritis nodosa confirming the earlier clinical diagnosis. Urinalysis showed 2 plus albumin, 2 erythrocytes, occasional leukocytes and many granular and hyaline casts per high power field. Cephalin flocculation tests were persistently 4 plus. Blood urea nitrogen remained above 40 mg. per cent, with non-protein nitrogens 84, 90, 92, 91, 116, 73, 78 and—pre-terminally—112 mg. per cent. Other total proteins were 5.4 Gm. per cent, with albumin/globulin ratio of 2.7/2.7 and 6.4 Gm. per cent, with albumin/globulin ratio of 2.9/3.5. The amount of spontaneously precipitable protein observable varied from a small sediment to a relatively heavy deposit, but it was always indisputably present. The patient died in a uremic state on the seventy-second hospital day, May 20, 1948. Permission for autopsy was refused.

It is noteworthy that in this case the putative diagnosis of polyarteritis nodosa was made shortly after admission to the hospital on the basis of the appearance of a spontaneously precipitable protein in a patient with bizarre complaints. This diagnosis was made before the characteristic clinical course was observed and before confirmatory biopsy was obtained in a patient who had been carefully studied during the course of many admissions to another hospital.

METHODS AND MATERIALS

Blood drawn in the morning before breakfast was allowed to clot at room temperature for several hours. The serum was separated by centrifugation. All sera were stored overnight in the refrigerator at 4°C.

Electrophoretic studies on the precipitate were carried out in a double-section Tiselius microcell (2 ml. capacity) at a concentration of 0.5 per cent. The electrophoretic study was made at pH 11.7, using a glycine-sodium hydroxide Sørensen buffer. At this pH the precipitate was judged sufficiently soluble for electrophoretic analysis. As a control a known sample of gamma globulin was run to determine its mobility under the same given conditions as the precipitate. This micro run also served to demonstrate the practicality of using the Sørensen buffer for electrophoretic studies. Runs on the precipitate were of 162 minutes duration, an adequate time interval for separation and measurement of the fractions involved. Electrophoretic studies on the supernatant sera after removal of the precipitate were carried out in a double-section Tiselius cell (11 ml. capacity) using a pH 7.6 phosphate buffer (ionic strength 0.2). Electrophoretic studies without dialysis on fresh serum—before and after spontaneous precipitation—were likewise carried out.

Microchemical analyses of the precipitate were carried out as follows: The precipitate with its supernatant serum was centrifuged at 1,500 revolutions per minute at 2°C. The precipitate was washed with 5 ml. of water at 2°C. and recentrifuged. The same washing procedure was repeated and the precipitate was resuspended in water and lyophilized. Nitrogen determination was done colorimetrically by Nesslerization. Phosphorus was determined by the method of Fiske and SubbaRow.

OBSERVATIONS

The amount of precipitate found varied in all six patients, as well as in any one patient under different conditions. The following preliminary chemical and physical characteristics were common to all precipitates in all six patients: (1) Maximum precipitation occurred after twenty-four hours, with little or no precipitation there-

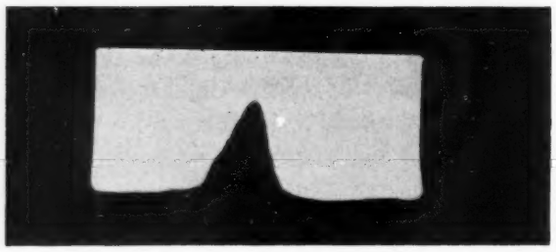
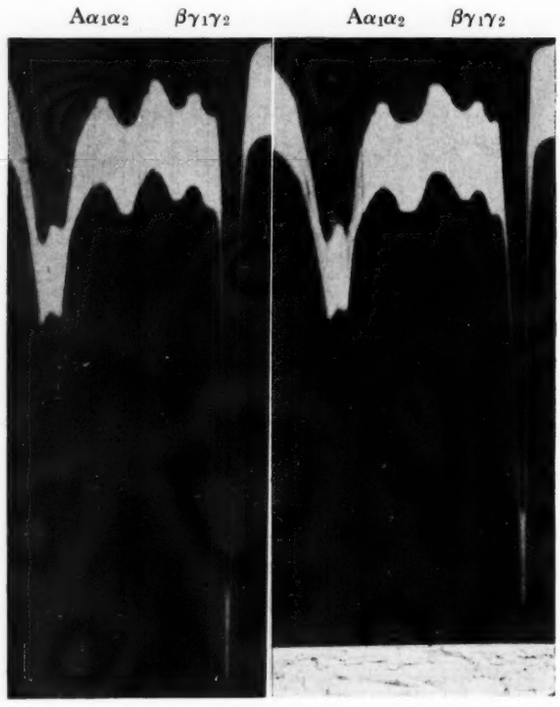


FIG. 1. Electrophoretic pattern (descending boundary) of the irreversible precipitate in Case VI.

after. (2) On warming the serum to room temperature the precipitate did not redissolve. (3) No precipitation or turbidity was induced on centrifugation of serum at room temperature. (4) The precipitate gave a positive xanthoprotein reaction with concentrated nitric acid. (5) The precipitate cleared on heating slowly in a water bath at about 70°C., and coagulated at about 80°C. (6) It was not soluble in distilled water or in 0.9 per cent sodium chloride. (7) On attempting solution in 0.01 sodium hydrochloric acid a cloudy solution—or, appropriately, a suspension—resulted from which no reprecipitation could be obtained on standing or on centrifugation. (8) A precipitate was noted on treating the suspension first described with 22.2 per cent sodium sulfate (Howe's method).

As a result of these preliminary examinations we were able to define the precipitate as a protein and specifically as a globulin.

Various technical and practical difficulties prevented quantitative and electrophoretic studies in our first five patients. In the sixth patient these studies were performed with the following results: (1) The dry weight of the precipitate was 0.08 Gm. per 100 ml. of serum. This value varied in the same patient in different stages of the disease. (2) The precipitate obtained by centrifugation of the serum in the cold followed by several water washings was increasingly soluble at increasing pH in the range studied (pH 7 to pH 12). It was judged sufficiently soluble at pH 11.7 for an electrophoretic run. (3) Results of the electrophoretic run on the precipitate (Fig. 1) showed it to be a nonhomogeneous substance with a large slowly



2A 2B

FIG. 2. Electrophoretic patterns (ascending boundaries) of fresh serum (A) before any precipitation and (B) after removal of precipitate in Case VI.

moving component and at least one fast moving component. The calculated mobility for the large component was 5.7×10^{-5} cm^2/volt/second, and for the smaller one 7.5×10^{-5} cm^2/volt/second. All calculations were based on the descending boundaries. (4) Microchemical analyses of the precipitate showed the nitrogen content to be 13.9 per cent and the phosphorus content to be 0.16 per cent. (5) Electrophoretic analysis of the supernatant serum after withdrawal of the precipitate for electrophoresis revealed the following distribution of components in percentage concentration:

Total protein	6.4 Gm. %
Albumin	37% (normal, 57.5%)
Alpha globulin	10% (normal, 14.4%)
Beta globulin	11% (normal, 16.5%)
Gamma globulin	42% (normal, 11.7%)

Electrophoretic analysis of fresh undialyzed serum before precipitation, and analysis performed after precipitation revealed the following distribution, utilizing the ascending limbs of both curves. (Fig. 2.)

	Albumin	$Alpha_1$	$Alpha_2$	Beta	$Gamma_1$	$Gamma_2$
Before precipitation, (% concentration)	33.8	5.8	7.7	12.3	18.8	21.6
After precipitation, (% concentration)	37.8	6.2	8.0	11.6	24.0	12.4

COMMENTS

The precipitate described herein differs from that noted by Stein and Wertheimer[1] who reported a precipitate which redissolved at room temperature. This did not occur in our patients. In a follow-up report Wertheimer and Stein[2] described a precipitate which they termed the "cold fraction," to indicate that protein portion of serum which precipitates when the serum stands for twenty-four hours at 7° to 11°c. In most instances reported by these workers the precipitate redissolved at room temperature. Our precipitate has the same characteristics as the "cold fraction" plus one additional feature—precipitation is irreversible on rewarming to room temperature. In this respect this fraction is also unlike those reported by Lerner and Greenberg,[3] Atlas et al.,[4] Holmberg and Grönwall[5] and Shapiro and Wertheimer.[6] In addition it is unlike the cold-susceptible proteins precipitated in multiple myeloma, as reported by Bing,[7] Wintrobe and Buell[8] and Von Bonsdorff et al.[9] Lerner and Watson[10] and Lerner et al.[11] later introduced the term "cryoglobulin" and gave various physical and chemical data showing that their protein was not unlike a gamma globulin. Analysis of electrophoretic patterns and of results of the various chemical and physical investigations described for our precipitate would seem to indicate that it probably comprises one or more of the group making up the gamma globulin fraction.

The gamma globulin fraction has been found to contain many of the known antibodies. A rise in gamma globulin has been noted in many infectious diseases.[13,14] It is possible that the elevated gamma globulin found in our patients, all of whom were chronic cases, may be in the nature of a "reagin." In support of this postulate one of the etiologic factors in polyarteritis nodosa has been thought to be allergic in nature.

In our series of six patients Cases I, II and VI were definitely proved to be polyarteritis nodosa. In Case III exitus followed rapidly after admission to the hospital, leaving insufficient time for an adequate study. In view of the suggestive clinical and laboratory data the possibility of polyarteritis nodosa definitely cannot be eliminated. In Case V the possibility of polyarteritis nodosa is also strong.

SUMMARY

Studies were made on the serum of a proved case of polyarteritis nodosa in which the appearance of a spontaneous precipitate at 4°c. had been noted. The observed spontaneously precipitable protein differed from previously reported "cold fractions" or "cryoglobulins" in not redissolving at room temperature. Electrophoretic studies indicated that it is one component of the group of gamma globulins.

The observed spontaneously precipitable protein also appeared in other cases—but not always—in which there was a reversal of the albumin/globulin ratio in the presence of a strongly positive cephalin flocculation reaction and of azotemia. The total serum protein was not actually elevated but it was usually increased from a relatively low value to a normal or slightly high normal with progress of the disease.

Since this same type of precipitate had been observed in two other proved cases of polyarteritis nodosa, the suggestion is offered that polyarteritis nodosa should be suspected when an irreversible spontaneous protein precipitate appears in the serum of a patient with a bizarre clinical picture.

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Acute Diffuse Glomerulonephritis*

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A CENTURY separates us from Bright's classical description of the disease which bears his name; since then, many attempts at subclassification have been undertaken and several syndromes have been described, but the etiology and pathogenesis of the disease still pose many unsolved problems. Much of our present knowledge is based on clinical studies from the first World War when acute nephritis occurred in soldiers in epidemic proportions. In the laboratory, however, many recent discoveries have been made, both in the field of renal physiology and as a result of the experimental production of acute nephritis in animals. We are faced with a wealth of facts but correlation lags behind.

Anticipating a possible epidemic of "trench nephritis" in the recent war, preparations were made at the 103rd British General Hospital in the field for planned clinical research. Although no epidemic occurred, a number of patients were studied and these studies seem to throw new light on some of the problems involved.

MATERIAL AND METHODS OF STUDY

The present report deals with sixty-two patients with acute glomerulonephritis, one with lipoid nephrosis and three with "nephritis with nephrotic syndrome," making a total of sixty-six. They were observed between May, 1943, and June, 1945, nine in North Africa and the rest in Italy. Only fourteen were direct admissions, the remainder being transferred from forward medical units. The patients were all soldiers, fifty-six from the United Kingdom, six from enemy prison camps and four from elsewhere.

Routine history reporting included a thorough inquiry into the patient's condition of health during the four weeks preceding the onset of acute nephritis. An ophthalmologist's opinion was obtained in the event of any suspected or obvious abnormality of the eyegrounds. A fluid-balance chart was maintained on all patients. The blood pressure, urinary deposit and erythrocyte sedimentation rate were checked about once a week, more frequently or daily when in a phase of rapid change. Hemoglobin (Sahli), hematocrit values, and serum proteins (copper sulfate method) were estimated occasionally.

The following tests were used for the assessment of renal functions: (1) Dilution. The patient, after emptying his bladder, drank 2 pints of water within one-half to three-quarters of an hour. Specimens of urine were then collected hourly over the next four hours. The test was considered satisfactory if the total volume of urine passed exceeded 900 cc. and if the specific gravity dropped to 1.002 or below. (2) Concentration. Fluid deprivation was carried out for thirty-six hours, ending at 6 A.M. Normal concentration was indicated by a rise in specific gravity to at least 1.028. (3) Blood urea. Values up to 40 mg. per cent were considered normal. (4) Urea clearance. (5) Endogenous creatinine clearance. As inulin, considered to be a non-threshold substance with a clearance equal to the glomerular filtration rate, was unobtainable in the field, endogenous creatinine clearances, which are thought to be sufficiently near this value to warrant conclusions, were estimated instead. The amount of creatinine in the specimens was measured by the method of Popper, Mandel and Mayer[1] using a photoelectric colorimeter. The usual test consisted of three-hourly readings over a period of twenty-four hours, the curve so constructed giving a clearer picture of events than a single reading over a short time.[2] Normal curves exhibit marked fluctuations, the rate of filtration varying between about 80 and 180 cc. per minute; the higher readings usually occur during the first

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part of the day, the lower ones at night. Tubular reabsorption of water was calculated by subtracting the known volume of urine from the estimated volume of glomerular filtrate in unit time and is expressed as a percentage of the filtrate. In normal subjects this percentage is

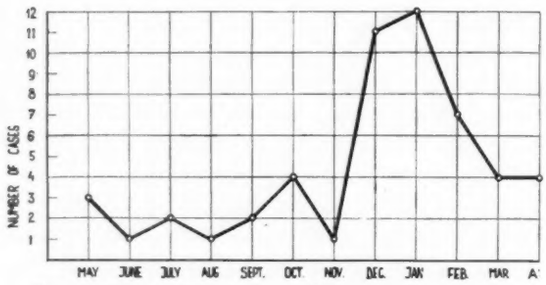

FIG. 1. Seasonal incidence of glomerulonephritis.

remarkably constant, being close to 99 per cent and rarely falling below 98.3 per cent unless the body is flooded with water. Reabsorption of 98 per cent of the filtrate is equivalent to a U/P ratio of 50, 99 per cent to a U/P ratio of 100 and 99.5 per cent to a U/P of 200.

HISTORY

Table 1 shows the incidence and nature of preceding infection in those of the present series. Some infection was found in fifty-eight of sixty-six cases, 87.8 per cent. The significant period was considered to be the thirty days preceding the onset of nephritic symptoms. The term "infection" includes simple sore throat, coryza, septic skin conditions and diarrhea, the last often being due to Flexner or to allied bacilli prevalent in the Mediterranean area. In a control series of one hundred unselected hospital patients a past history of infection during the same interval was present in 46 per cent. Tonsillitis and infections of the upper respiratory tract were most frequent. This probably accounts for the high incidence of acute glomerulonephritis during the winter quarter (Fig. 1), thirty of fifty-two patients seen between May, 1944 and April, 1945 presenting themselves between December and March.

The interval between the beginning of the infection and the first manifestations of acute glomerulonephritis averaged 16.5 days. The figures represent the upper limit as the interval has been calculated from the first day of the preceding infection. Moreover, there is probably a time-lag between the first clinical manifestations of nephritis and the onset of the disease. One patient (Case 47) had an extensive vascular nevus involving the whole of the right upper limb and shoulder girdle. Sore throat occurred on January 1, 1945, and on the 14th he complained of lassitude and slight breathlessness on exertion. Eight days later the part of the body affected by the nevus became edematous, but edema did not become generalized until seven days later, i.e.,

TABLE 1

INCIDENCE AND NATURE OF PRECEDING INFECTION IN ACUTE GLOMERULONEPHRITIS

Preceding Infection	No. of Patients	Per cent	Longest Interval	Shortest Interval	Average Interval
Tonsillitis	23	34.8	30 days	0 days	15.6 days
Coryza	16	24.3	30 days	2 days	18.3 days
Diarrhea	10	15.1	30 days	1 day	16.0 days
Septic skin	5	7.6	30 days	5 days	16.3 days
Alveolar pyorrhea	1	....	Present for 3 months		
Pansinusitis	1	....	Present for 12 years; operation 7 days previously		7 days
Bronchopneumonia	1	....	.....	.....	5 days
Gonorrhea	1	....	.....	.....	2 days
No history of infection	8				
Total No. of patients	66	87.8	30 days	0 days	16.5 days
History of infection	58				

fifteen days after the first symptoms and twenty-nine days after the onset of tonsillitis. It is clear that the tendency toward edema was present one week before it became obvious in those parts of the body where the capillaries were not, *a priori*, abnormal.

An interesting feature was the association of acute glomerulonephritis with typical rheumatic fever in six instances. The latter preceded the first manifestations of nephritis by fourteen to seventeen days in four patients, followed them by thirteen days in the fifth and commenced simultaneously with nephritis in the sixth. Two of these patients had Schoenlein-Henoch's rheumatic purpura and another developed urticaria four days before onset of the first symptoms of acute glomerulonephritis.

CLINICAL FEATURES

Tables II and III summarize the symptoms and signs encountered, with their relative frequency, time of appearance and duration

General Constitutional Symptoms. These symptoms were present to some extent in the majority of subjects. Headache occurred in about one-half, backache in about one-third and lassitude in one-fifth; these symptoms could not be traced to any specific phase of the morbid picture. Nausea and vomiting, which occurred at the onset in six patients, were always associated with an increased blood urea concentration although the reverse was not true. Vomiting

TABLE II
PRESENTING SYMPTOMS OF ACUTE GLOMERULONEPHRITIS IN ORDER OF FREQUENCY

Symptom	Incidence	
	No.	Per cent
Edema	49	74.2
Dyspnea	42	63.6
Headache	32	48.0
Macroscopic hematuria	26	39.3
Backache	22	32.0
Oliguria (observed by the patients)	13	19.6
Lassitude	13	19.6
Exaggerated thirst	11	16.0
Fever	9	13.6
Frequency	7	10.0
Vomiting	6	9.0
Dysuria	3	4.5
Epistaxis	2	3.0

TABLE III
SIGNS OF ACUTE GLOMERULONEPHRITIS

Sign	Incidence		Present at Onset	Appeared Subsequent to Onset	Subsided	In Instances in Which It Subsided		
	No. of Instances	Per cent				Shortest Duration (days)	Longest Duration (days)	Average (days)
Oliguria	47	71.2	47	..	45	7	54	21.5
Anuria	2	3.0	1	1	2	1	2	
Albuminuria	66	100.0	65	1	8	10	145	64.0
Hematuria	64	96.9	64	..	20	14	167	72.4
Granular casts	58	87.8	47	5	25	5	139	51.7
Edema	60	90.0	55	5	52	2	122	34.8
Pleural effusion	3	5.0	3	..	3			
Pericardial effusion	1	.....	1	..	1			
Ascites	1	.....	1	..	1			
Hypertension	57	86.3	51	6	55	7	140	37.6
Dyspnea	43	65.1	42	1	43	7	90	20.3
Pulmonary edema	8	12.1	5	3				
Hypertensive encephalopathy	3	4.5	..	3				
Retinal changes	7	10.0	..	..	5			
Raised non-protein nitrogen	23	71.9	21	2	23	?	70	

also heralded all attacks of hypertensive encephalopathy.

Oliguria. Oliguria was noted at the onset in three-quarters of the patients. Anuria lasting one to two days occurred in only two instances.

Urinary Findings. Albuminuria, hematuria and casts were usually persistent and in the majority of patients were still present when they were evacuated. Granular casts and renal epithelial cells were present in the urine at the onset in over fifty patients. Dysuria and frequency occurred in twelve patients. All of them had marked albuminuria and macroscopic hematuria and in addition four had a moderate number of pus cells.

Edema. Edema had the usual features of a "nephritic" hydrops; it was accompanied three times by clinically identifiable pleural effusion, once by pericardial effusion and once by ascites. On the average it lasted 34.8 days and subsided in all but the three patients with "nephritis with nephrotic syndrome." It was frequently the first manifestation of disease, but in eleven patients it followed other symptoms by four to twenty-one days.

Hypertension. Hypertension was present in fifty-seven patients and was maintained for an average of 37.6 days; it was usually mild or moderate but reached 200 mm. Hg systolic or above in nine patients. The highest reading was 215/130 mm. Hg. It was accompanied by some degree of breathlessness in forty patients; dyspnea occurred independently only twice and was associated with gross edema. While no regular relationship could be established between breathlessness and edema, there was no doubt about the relationship between breathlessness and hypertension. In most instances it occurred only on exertion and disappeared shortly after the patient had been put to bed, but five patients developed acute pulmonary edema and three had numerous basal rales. Excluding two patients in whom there was reason to suspect previous hypertension, no signs of left ventricular hypertrophy were found. Electrocardiograms were taken occasionally and were within normal limits.

Hypertensive Encephalopathy. Hypertensive encephalopathy complicated three instances of the disease and occurred on the seventh, twelfth and fourteenth day. It was heralded by severe headache, vomiting and a sharp rise in blood pressure. Two of the patients had one attack only, the third had three attacks. One was treated with venesection, the other two with sedatives and all recovered promptly.

Retinal Changes. Retinal changes were observed in seven patients. All had considerable hypertension, ranging from 175/100 to 205/130 mm. Hg. Two had retinal hemorrhages only, three had papilledema and two presented a typical picture of "hypertensive neuroretinopathy." The fundi in those patients with only hemorrhages or papilledema returned to normal while the patient was still under observation, whereas "hypertensive neuroretinopathy" persisted and was still present in the two patients so afflicted when they were evacuated, several months after the acute stage had subsided and long after the blood pressure had returned to normal. In all other respects both patients seemed to have typical acute glomerulonephritis; there was no evidence of a previous attack or of previous hypertension; routine urinary examination was said to have been performed on enlistment with negative results.

RENAL FUNCTION TESTS

Blood Non-protein Nitrogen. The blood non-protein nitrogen was elevated at the onset in twenty-three of the thirty-two patients in whom it was determined; in about one-half of them it quickly returned to normal but remained elevated after one month in eight patients and after sixty days in four.

Dilution Test. This test usually demonstrated fluid retention in the initial stage. Although slight diuresis, with a fall of specific gravity to 1.002 or below, was usually detected during the first hour or two, this soon stopped and the total output

was below normal. This behavior suggests that the failure to dilute at this stage was not due to the kidneys, which evidently responded properly to the stimulus, but to changes in fluid balance. In the later stages similar behavior was encountered in eight patients, pointing again to fluid imbalance.

2. All the patients recorded here were in satisfactory fluid balance. In the group with renal epithelial cells or granular casts in the urinary deposit, which are indicative of a severe degenerative process in the tubular epithelium,[3] satisfactory concentration was achieved only four times in seventy in-

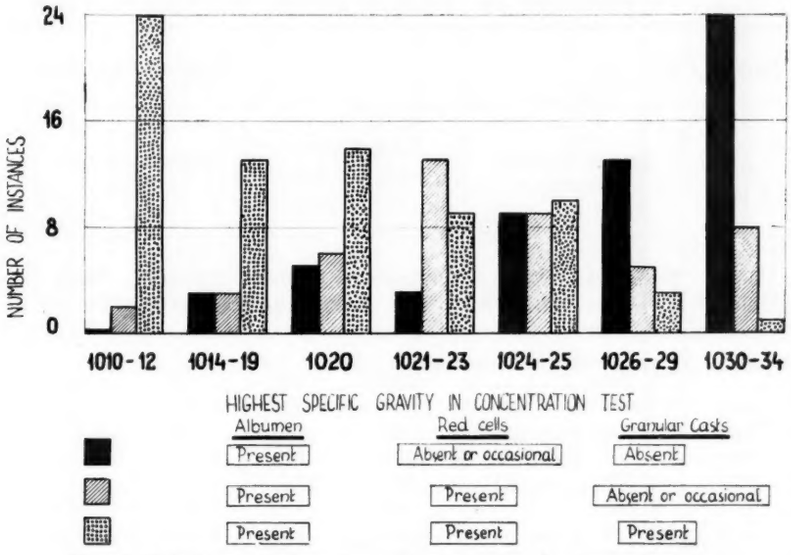

FIG. 2. Relationship of concentrating power and urinary findings.

No response to fluid ingestion occurred in five patients and the specific gravity of the urine remained fixed. In these patients there was additional evidence indicating serious renal damage.

Only fifteen patients in the whole series showed an impaired water dilution test, which may be related to the relatively small proportion of direct admissions.

Concentration Test. On the other hand, the concentration test revealed impaired function in forty-three patients, even as early as the third day. Improvement in this respect was poor and slow, the figure remaining virtually unchanged until final disposal in twenty-four patients and returning to normal in only nine; in ten there was some improvement over the period of observation and in six there was deterioration. All five patients who were unable to dilute had very restricted concentrating power, in four amounting to isosthenuria. That loss of concentrating power is directly related to tubular damage can be seen from Figure

stances while in the group with only albumin and/or erythrocytes in the urine, both of which are thought to be of glomerular origin, normal concentrating power was recorded in twenty-seven of fifty-six instances.

As both dilution and concentration are functions of the renal tubules, the greater impairment of concentrating power needs explanation for thirty-eight patients with impaired or abolished concentrating power diluted normally. The discrepancy is probably due to dissociation of these two tubular functions, concentrating power being impaired in renal disease earlier than diluting power. Evidence is accumulating that the concentrating power depends upon the functional integrity of the distal tubule, the water re-absorption of the proximal tubule proceeding isosmotically,[4] a process for which Smith[5] suggested the name of "obligatory reabsorption." This process normally accounts for the conservation to the body of about 87 per cent of the water

filtered through the glomeruli. It is, however, in the distal tubule that by a process of "facultative reabsorption" the remaining 13 per cent of the filtrate undergoes an osmotic change, water reabsorption proceeding against the osmotic gradient created by urea, salt and other unreabsorbed substances. It is this distal tubular segment which seems to respond to the requirements for water, conserving up to 99.8 per cent of the filtrate in cases of dehydration and rejecting up to some 13 cc. of every 100 cc. of filtrate under conditions of maximum hydration. This function is to a great extent, but not entirely,[6] under the influence of the antidiuretic hormone (ADH) of the posterior lobe of the pituitary. The poor results of the concentration test consequently could be due either to failure of the pituitary to respond to conditions of dehydration or to a lack of sensitivity or inability of the distal tubular cells to respond to the stimulus of an antidiuretic hormone.

To examine the matter further fifteen patients with poor concentrating power were submitted to a second concentration test, during which 1 cc. of pituitrin was injected subcutaneously every two hours. Sensitivity to the antidiuretic action of pituitrin was previously established by observing its effects on the dilution test. In all instances tested pituitrin could prevent water diuresis. (Table IV.) The maximum concentrating power, however, remained unaffected and in a few instances was slightly less with pituitrin than without its use. The total output of urine in the concentration test diminished further under the influence of pituitrin only in one-half of the patients, indicating that in the remainder the tubules may have been subjected to the maximum effect of endogenous ADH during the first concentration test without pituitrin.

From these observations it may be inferred that the inability to concentrate in acute nephritis is not due to some disturbance in the secretion of the ADH nor is the distal tubule insensitive to the antidiuretic action of this hormone. Further

TABLE IV

EFFECT OF PITUITRIN ON IMPAIRED POWER OF CONCENTRATION

Case No.	Dilution Test				Concentration Test				
	Total Volume of Urine (cc. excreted in 4 Hr.)		Lowest Specific Gravity		Total Volume of Urine (cc. in 24 Hr.)		Highest Specific Gravity		Maximal Reabsorption in Per cent of Glomerular Filtrate
	Ordinary Test	With Pituitrin	Ordinary Test	With Pituitrin	Ordinary Test	With Pituitrin	Ordinary Test	With Pituitrin	
33	755	...	1.000	.....	1840	1390	1.024	1.019	99.5
32	1000	210	1.000	1.020	890	530	1.018	1.020	99.6
28	850	230	1.000	1.016	1060	860	1.020	1.020	99.5
51	800	400	1.000	1.010	1010	980	1.020	1.016	99.4
47	640	390	1.000	1.015	1345	1125	1.014	1.016	99.0
49	1025	220	1.000	.....	560	790	1.024	1.017	99.5
45	915	315	1.000	.....	1035	540	1.020	1.022	99.5
43	1000	250	1.000	1.010	1600	1050	1.024	1.018	99.4
52	1280	240	1.000	.....	940	900	1.016	1.015	99.7
34	1030	...	1.000	.....	1295	1310	1.020	1.015	99.3
37	1035	285	1.000	1.016	1090	1050	1.018	1.022	99.3
31	1000	...	1.000	.....	1240	1065	1.015	1.015	99.0
39	1750	...	1.000	.....	850	1090	1.022	1.024	99.3
56	1525	...	1.002	.....	700	700	1.020	1.020	99.5

evidence that there is no failure to reabsorb water in acute nephritis will be presented later. The loss of concentrating power therefore points to impairment of the osmotic function of the distal tubule alone, which suffers long before there is any reduction in the capacity to dilute.

With organic destruction of glomeruli, as seen in chronic nephritis, the filtration rate falls below the normal level and to maintain as normal a function as possible all the available glomeruli have to function continuously at a maximum rate;[8] variations are minimal and the curve is rigid. (Fig. 3c.)

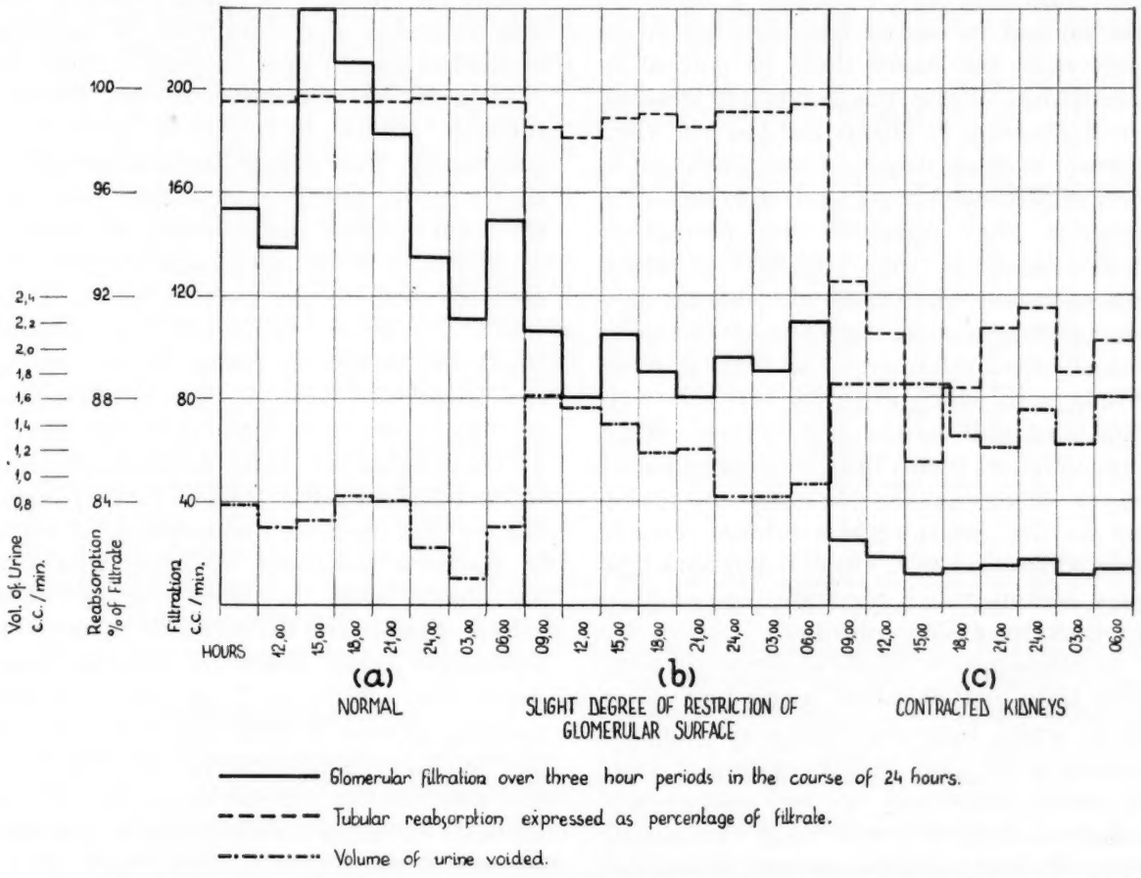

FIG. 3. Curves of glomerular filtration, tubular reabsorption of water and diuresis over a twenty-four-hour period; *a*, normal kidneys; *b*, slight degree of restriction of glomerular surface; *c*, contracted kidneys.

Endogenous Creatinine Clearance. Creatinine clearance was measured over successive three-hour periods for twenty-four hours in seventy-nine instances and on forty-seven patients. Smith[7] has deduced from observations of glucose Tm on normal human kidneys that there is probably no reserve of active glomeruli. The extent of glomerular activity depends, however, on hemodynamic changes in the kidney and varies according to the body requirements. Consequently, curves of glomerular activity constructed over a twenty-four-hour period will show marked fluctuations. (Fig. 3A.) This may also happen in acute glomerulonephritis when sufficient numbers of glomeruli are out of action. In these patients significant elevation of blood urea above 40 mg. per cent did not occur until glomerular filtration was fixed below 50 cc./min. In less severe cases, as judged by other tests, the level of glomerular filtration was somewhere near the lower limit of normal and in milder cases fluctuation appeared (Fig. 3B), suggesting a variability in glomerular activity. In our series filtration was invariably normal (fourteen instances) when there was albuminuria alone

or with slight hematuria but no granular casts, and when the concentration test was normal. When granular casts were associated with similar findings, filtration was normal in eight instances and relatively fixed in the neighborhood of the lower limit of the normal in five. When impaired concentration was present, however, filtration was normal in twelve instances, relatively fixed near the lower limit of normal in twenty-one, below this limit but showing fair fluctuation in fifteen and low and rigid in four; in other words, it was abnormal in forty of fifty-two instances. It is to be noted, however, that filtration was normal in twelve instances (ten patients) in which concentration was impaired, whereas concentration was never normal when filtration was impaired although it was normal in five instances in which filtration was relatively fixed but still within the normal range. This indicates again that the concentrating power is a very sensitive function and probably the first indicator of a tubular disturbance which, as Earle, Taggart and Shannon[9] have demonstrated, generally accompanies a reduction of filtration rate.

In following the course of sixteen patients with impaired filtration when first measured, serial filtration curves returned to normal within one to four months in eight instances, improved in two others and remained more or less static in the remainder. Of those whom returned to normal, five still had granular casts and two also showed impaired concentration. When filtration curves remained fixed although not necessarily below the lower limit of the normal, granular casts were always found, and impaired concentration occurred in six of eight patients. Nor was it possible to predict the course of filtration by the nature of the filtration curve; thus two patients with initially rigid and low values returned rapidly to normal, and the tendency toward recovery was the same whether early filtration levels were low but retained fluctuation or whether they were within normal limits but relatively fixed.

Total Tubular Reabsorption. Tubular reabsorption of water was calculated from the filtration rate and urine flow in all instances. Its reduction and increase in variability is one of the most constant features in chronic nephritis in which glomeruli have lost all adaptability and the only remaining regulating mechanism is tubular. (Fig. 3c.)[2] Chasis and Smith[10] produced evidence that this reduction of reabsorption in nephritis is attributable in part to reduction in the "obligatory" reabsorptive process, perhaps through failure to reabsorb electrolytes proximally, thus producing osmotic diuresis. In acute glomerulonephritis, however, the total tubular reabsorption of water is usually normal and was found so in 80 per cent of those in the present series. Even when abnormal, reduction was usually slight and rarely fell below 96 per cent of the filtrate (U/P = 25). We have pointed out the failure to concentrate is not due to an inability of the distal tubule to respond to an ADH stimulus. This is further borne out by our data on reabsorption of water in fourteen instances of acute glomerulonephritis with impaired concentrating power. (Table IV.) In all cases tubular reabsorption could reach the normal maximum level (99 to 99.7 per cent). Consequently, in none of them was there a failure of "facultative reabsorption" of water, but this process lost its efficiency due to the inability of distal tubular cells to produce osmotic work.

Urea Clearance. Urea clearance provided little additional information to that given by the filtration curves. In few instances was it found below 60 per cent of the normal average and never below 40 per cent. Goldring and Chasis[11] have shown that on a constant protein diet the blood urea varies inversely with the urea clearance, as it should in theory. Conditions in a military hospital, however, made it impossible to eliminate all the possible factors which tend to obscure this relationship.

OTHER TESTS

As seen in Figure 4 the erythrocyte sedimentation rate (E.S.R.) was almost in-

variably raised in the initial phase, often considerably. It fell to lower levels in harmony with clinical improvement but reached normal only when the patient was cured or left with but minor urinary changes. Some of the curves show a clear division into two phases: the first sloping steeply downward in association with relatively rapid subsidence of hypertension and edema, the second rather horizontal and parallel with the much slower improvement in concentration and urinary findings. The degree of acceleration of the E.S.R. in this latter part of the graph was proportional to the severity of the renal lesion, being highest when renal function was grossly impaired and abnormal ingredients in the urinary deposit were conspicuous, and lowest when renal function was normal and the urine showed little but albuminuria. (Fig. 5.)

The blood picture was rarely altered, hemoglobin being below 80 per cent on five occasions and below 70 per cent once. Slight polymorphonuclear leukocytosis was detected occasionally at the onset. Observations on serum proteins and hemocrit values were too few to warrant any conclusions.

PARTIAL SYNDROMES

While the great majority of cases were characterized by transient hypertension and edema, by impaired glomerular filtration with or without retention of non-protein nitrogen, by hematuria and albuminuria and by poor concentration and granular cases in the urine, i.e., by all the well known features of the disease, a limited number of patients revealed or developed only part of the picture. As it is thought that these instances throw light on the pathogenesis of acute glomerulonephritis they will be described in more detail:

Hypertension and Edema without Nephritis:

CASE 18. The patient was a man aged twenty-eight. He had been treated in this hospital for hiccough thought to be due to basal pleurisy in April, 1944. On June 10, 1944, he developed breathlessness on exertion. On the 15th he noticed a "blotchy" rash on both legs which subsided after forty-eight hours. On the 17th painless swelling appeared in both legs and three days later his face became puffy and he was admitted to the hospital.

On examination his temperature was 99.2°F.

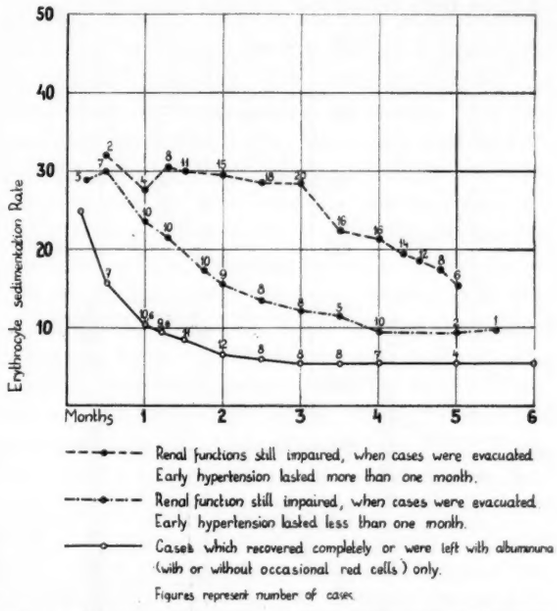

FIG. 4. Progress of changes of the erythrocyte sedimentation rate in the course of the disease, grouped according to the duration of the acute stage and the final outcome.

His face, sacrum and both legs were edematous and his blood pressure was 170/95. Venous pressure was normal and no abnormality was detected in the heart, lungs, central nervous system or ocular fundi. Contrary to expectation, examination of the urine disclosed no abnormality; there was no albumin and no abnormal elements were found in the urinary deposit. The E.S.R. was 14 mm. (Wintrobe), white blood cells numbered 5,350 per cm. (polymorphonuclears, 47 per cent, lymphocytes, 52 per cent; monocytes, 1 per cent) and blood urea, 28 mg. per cent.

He had marked oliguria, passing on June 22nd only 100 cc. of urine in twenty-four hours. He was treated by a forty-eight-hour period of complete food and fluid starvation (June 21st and 22nd), followed by a period of restricted fluid intake and low protein diet. Hypertension persisted until June 23rd; on June 24th it fell to 145/85 and on the 25th to 135/90 and eventually settled around 105/70. Parallel with its fall, edema started to disappear and diuresis increased correspondingly, the volume of urine exceeding the fluid intake by 1,100 cc. on

June 26th. The subsequent course was uneventful and he was clinically normal by the first week of July although a faint trace of albumin could be detected occasionally in the urine. Repeated examinations of the urinary deposit revealed no abnormal ingredients and all routine renal function tests remained normal throughout.

developed general malaise and lassitude. Five days later he had a rigor and was sent to the hospital. On admission the temperature was 100°F. and a blood smear revealed moderate Plasmodium vivax infection. The urine, however, contained obvious blood, and microscopic examination revealed many granular and ery-

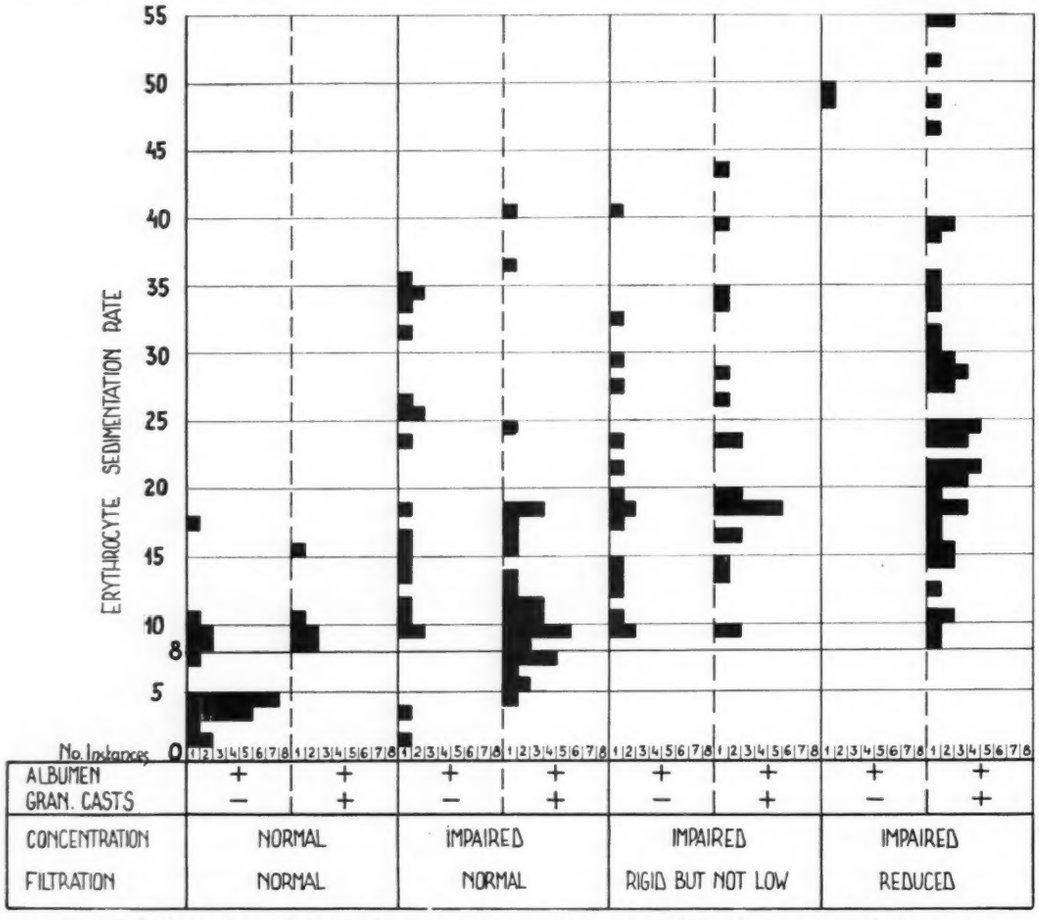

FIG. 5. Relationship of the erythrocyte sedimentation rate and the degree of renal changes.

Here then was a patient with oliguria, edema and hypertension who in the last two respects behaved like a patient with acute glomerulonephritis, yet in whom there was no evidence of renal involvement at the height of these manifestations; in the subsequent course, very slight and occasional albuminuria indicated that glomerular capillaries were rendered slightly more permeable by the pathologic process.

Acute Nephritis without Hypertension or Edema:

CASE 14. The patient was a man aged thirty-four. He had a sore throat during the first week of July, 1944. On August 6th he

throcyte casts. There was no edema; blood pressure was 100/65; blood urea was 48 mg. per cent. Fever responded to routine quinine and mepacrin therapy but the urinary findings persisted unabated. The urine output was markedly below the fluid intake which was maintained at 3 pints daily on account of malaria. On August 18th the volume of urine was only 250 cc. in twenty-four hours, but edema could not be detected. Both dilution and concentration tests gave highly abnormal results; there was no attempt at diuresis following 2 pints of ingested fluid and the highest specific gravity in the concentration test did not exceed 1.016.

Macroscopic hematuria subsided by the end

of August, but albuminuria and microscopic hematuria with granular and epithelial casts persisted throughout the four-months period of observation. At the time of the patient's evacuation to the United Kingdom toward the end of December, 1944, renal functions were still grossly impaired; the highest specific gravity of urine in the concentration test was 1.020, the lowest in the dilution test, 1.005; the blood urea was 50 mg. per cent and the urea clearance 58 and 62 per cent of the normal standard, with a rigid low curve of glomerular filtration around 50 cc. in one minute as measured by endogenous creatinine clearance; tubular reabsorption was still diminished, swinging between 95.8 and 98.6 per cent of the filtrate. Apart from poor concentration of dye, intravenous pyelography did not show anything abnormal and urine cultures were repeatedly sterile. Despite evidence of considerable renal damage, the blood pressure remained at 110/70 throughout and edema was never detected.

Case 37, admitted in January, 1945, was similar to Case 14. The picture was that of glomerulonephritis following febrile coryza, with urinary findings the same as in the previous patient. The highest specific gravity in the concentration test was 1.015 and there was marked oliguria; despite these findings there was neither edema nor hypertension. At this stage glomerular filtration was below normal and almost rigid, fluctuating between 55 and 85 cc./min.; tubular reabsorption was also lowered (96.3 to 98.5 per cent). The E.S.R. was 31 mm. per hour. After remaining in this condition for about two months the patient began improving slowly; the E.S.R. settled to normal levels in April, 1945, and at the time of his evacuation at the beginning of June, 1945, four months after the onset of his illness, he was left only with slight albuminuria and a few red cells and epithelial cells in the deposit; there was concentration to 1.028 and dilution was perfect; the filtration curve and tubular reabsorption became normal.

These two patients presented a picture of acute renal disease with all the characteristics of acute glomerulonephritis but in whom hypertension and edema were absent throughout in spite of severely impaired renal function and marked oliguria for at least seven days in both instances. Case 9 forms a link for it was similar to the last two except that in the fourth week of illness fleeting edema was detected in both legs.

The details of two other cases are also worthy of note:

Case 42. The patient, a man aged thirty-two, had several boils on his neck since March, 1945, and at the beginning of April developed hidradenitis axillaris. He became febrile on April 13th, with associated backache, and the next day he noticed that his urine was blood-stained and he complained of slight dysuria. On that day he was admitted to the hospital. The temperature was 101°F. Apart from the skin condition, physical examination revealed nothing abnormal; there was no edema and the blood pressure was 115/70. The urine contained albumin, large numbers of red cells, a few hyaline casts and renal epithelial cells. Urine culture was repeatedly sterile. White blood cells during the febrile stage numbered 6,900, 59 per cent being polymorphonuclears. After a few days the temperature settled and macroscopic hematuria subsided, but albuminuria with red blood cells, hyaline casts and scanty granular and epithelial casts in the deposits became a permanent finding and persisted at the time of his evacuation to the United Kingdom four months later. By then the boils had been healed for six weeks. Oliguria was absent throughout, the filtration curve was always normal, and only on one occasion, two weeks after the onset, was concentration power reduced, and then but slightly, the highest specific gravity reached being 1.025; four weeks later even this abnormality disappeared.

Case 39 was similar, except that no preceding infection could be traced. This patient was also febrile at the onset, had red blood cells and granular casts in the deposit, but no oliguria, no hypertension and no edema. The only functional abnormality was inability to concentrate above 1.024 during the second month of illness. At the time of his evacuation, five months after the onset, he still had marked albuminuria with microscopic hematuria and occasional renal epithelial cells in the deposit.

It is difficult to deny that these were instances of acute nephritis, especially as repeated urine cultures, blood counts and intravenous pyelograms were normal. All were soldiers who had had their urine examined on joining the Army and whose

physical condition had been repeatedly checked in the past.

It is possible to draw certain conclusions from these studies: First, it seems certain that hypertension, edema and oliguria can develop without evidence of a renal lesion. Second, a renal lesion having all the characteristic features of acute glomerulonephritis and accompanied by marked oliguria can develop without edema or hypertension. It follows that these two syndromes, although usually simultaneous, may exist independently of each other.

Nephrosis: Three patients will be described who were dominated by persistent edema and heavy albuminuria; the first two would ordinarily be regarded as examples of nephritis with nephrotic syndrome, the last as "pure nephrosis."

CASE 12. The patient, a Ceylonese aged twenty-six, fell ill September 10, 1944, with general malaise, fever and marked painless swelling of both legs, sacrum and face. He was admitted to the hospital on the same day. Apart from edema, investigation revealed nothing abnormal. The blood pressure was 100/65 and remained about the same throughout the period of observation. The urine was loaded with albumin and the deposit contained scanty red blood cells, hyaline casts and fairly numerous leukocytes and renal epithelial cells. Concentration was up to 1.026. The blood urea was not estimated at the onset but later was repeatedly about 30 mg. per cent. The initial edema tended to subside within the first four weeks but recurred in the sixth week and from then on remained stationary with minor variations throughout the three-months period of observation. The urine remained loaded with albumin and the deposit persistently showed about 5 red blood cells per high power field, hyaline and granular casts and renal epithelial cells. In spite of edema the dilution test was satisfactory on several occasions; concentration, however, deteriorated progressively, and shortly before evacuation the specific gravity of the urine could not be made to exceed 1.016. Total blood proteins were estimated at 4.8 Gm. per cent; the E.S.R. varied between 17 and 28 mm. in an hour.

CASE 58. The patient, a man aged twenty-nine, had slight puffiness of the face for four months before developing marked generalized edema associated with severe albuminuria; only a few red blood cells and occasional epithelial casts were found in the deposit. During the first three weeks of generalized edema the blood pressure was elevated, the highest reading being 170/105. Edema and urinary changes persisted for at least four months when the patient was evacuated. Plasma proteins measured 4.5 Gm. per cent, the blood cholesterol 280 mg. per cent. The concentration was 1.032 and, although the dilution was 1.002, be excreted only 605 cc. in four hours. The blood urea was 26 mg. per cent. Glomerular filtration was rather rigid but within normal limits, oscillating about 100 cc./min. Tubular reabsorption was high, 99.5 to 99.7 per cent of the filtrate.

CASE 4. The patient had typical lipoid nephrosis with marked albuminuria and extensive edema lasting for five months, with perfect renal functions and no hypertension. The urinary deposit contained hyaline casts but no red cells or other abnormal ingredients.

These patients form an interesting intermediate between diffuse glomerulonephritis and what is referred to as pure nephrosis. All had massive edema, heavy albuminuria and reduced plasma proteins. Case 12 showed impaired renal function and nephritic elements in the urinary deposit but no hypertension; Case 58 showed no impairment of renal function, minimal nephritic elements in the urinary deposit, but had transient hypertension; Case 4 showed normal renal function, had no nephritic elements in the urinary deposit and no hypertension. There can be no doubt that Cases 12 and 58 had acute glomerulonephritis. Had transient hypertension occurred in Case 12 instead of Case 58, the only difference between Cases 58 and 4 would have been the occurrence of a few red cells and occasional epithelial cells in the urinary deposit of the former. If the patient mentioned earlier with hypertension and edema only and no evidence of a renal lesion be rightly regarded as having the syndrome called acute glomerulonephritis, and considering the details of the patients presented illustrating all possible combinations of the various facets of this syndrome there seems

no valid reason to exclude Case 4. In other words, the evidence suggests that nephrosis is properly regarded as representing one aspect of the syndrome called glomerulonephritis.

COURSE

Hypertension subsided relatively quickly, usually within one to two months, in all but two patients in whom the rigidity and tortuosity of the brachial arteries associated with left ventricular dilatation and hypertrophy proclaimed previous essential or chronic nephritic hypertension. In one of these patients all evidence of nephritis disappeared while under observation; in the other considerable improvement had occurred in this respect when the patient was evacuated. The development of chronic nephritic hypertension was observed in only one patient, Case 33. In this patient the hypertension of the acute phase subsided in the usual time; there was an interval of three weeks during which the blood pressure was normal and the persistent hypertension developed while other features indicated established chronic nephritis.

Edema also subsided relatively quickly, usually within the same time as the hypertension, in all but four patients who presented the nephrotic syndrome; in three of them no gap between the early and chronic persistent phase was demonstrable.

In contrast to the behavior of hypertension and edema, impaired filtration, albuminuria, reduced power of concentration and granular casts in the urine were remarkably persistent. Thus, of fifty-three patients with primary acute cases commencing with hypertension, edema, impaired renal function and abnormal urinary constituents, only two remained in that category at the end of the second month; two remained edematous but not hypertensive; nine remained hypertensive but not edematous; four were cured; nine had abnormal urinary constituents only; the remaining twenty-seven had impaired renal function and abnormal urinary constituents but neither hypertension nor edema and twenty-five were virtually unchanged at the end of four months. This dissociation between the course of hypertension and edema on the one hand and that of altered renal function on the other is well illustrated in Figure 6.

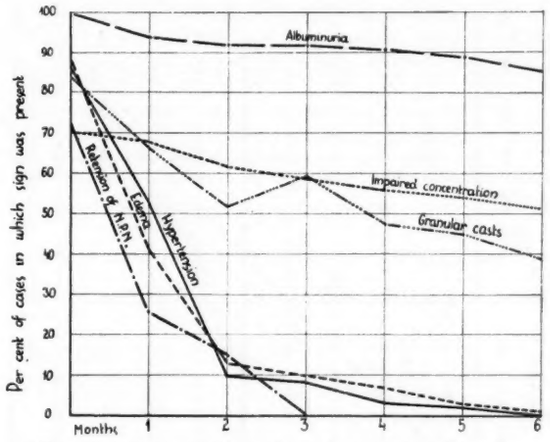

FIG. 6. Progress of the chief signs of the disease.

While the facts suggest that hypertension and edema are independent of the renal lesion, there is more evidence indicating that they are also independent of one another. Thus in Case 59 there was hyper-

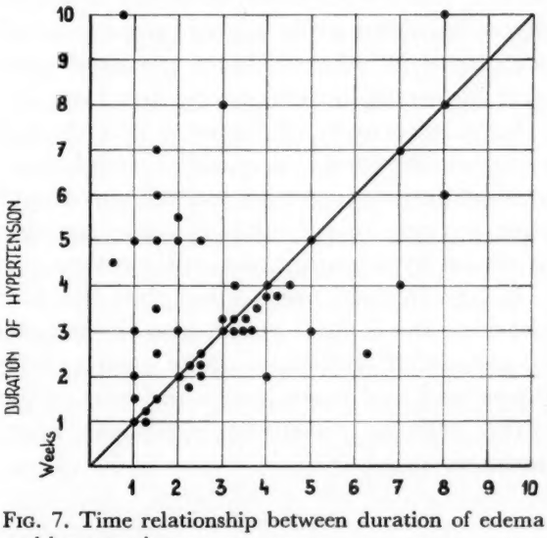

FIG. 7. Time relationship between duration of edema and hypertension.

tension but no edema; in Cases 12, 26, 58 and 60 there was edema but no hypertension; although in thirty-one instances both manifestations were closely associated, hypertension outlasted edema by one to nine weeks in fourteen instances and edema

outlasted hypertension by two to three and one-half weeks in five instances. (Fig. 7.)

Oliguria, of course, is necessarily intimately linked with edema. Yet even here partial dissociation can be demonstrated. (Fig. 8.) In addition to those patients (Cases

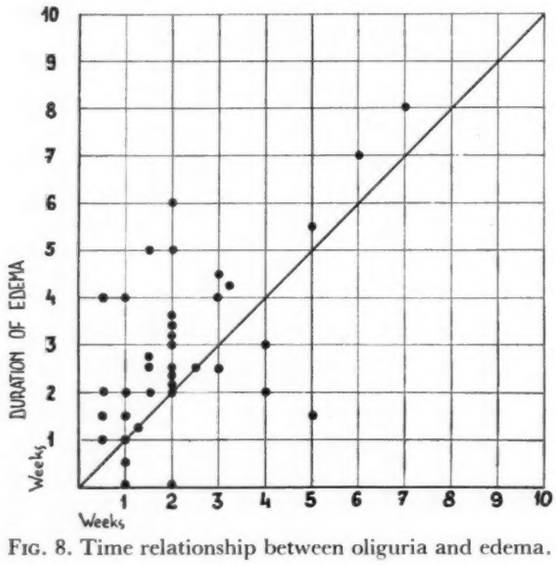

FIG. 8. Time relationship between oliguria and edema.

14 and 37) in whom marked oliguria for seven days failed to result in detectable edema, there were other instances in which edema subsided while oliguria persisted and yet others in whom edema persisted long after the establishment of good fluid balance.

Further scrutiny of Figure 6 reveals that nitrogen retention runs parallel with hypertension and edema and indeed was found after the first month only in those patients in whom hypertension was still present.

It has already been noted that the first phase of the E.S.R. graph also appears to be associated with these acute events while the second and more horizontal part of the curve reflects relatively persistent renal damage.

PROGNOSIS

There are few diseases in which reports on prognosis have differed so widely. On the whole the recovery rate is inversely proportional to age and perhaps to the accuracy and number of tests employed in its assessment. Figures for several series of cases occurring among soldiers in the first world war were more constant: Hume and Nattrass[12] recorded 45 per cent cured, Magnus-Alsleben[16] 40 per cent and Longcope[14] 41 per cent.

In the present series of sixty-six patients followed for an average period of observation of 123 days, only eight (12 per cent) recovered while under observation. Another probably recovered but had persistent hypertension. The remainder were evacuated while still showing evidence of disease. There were no deaths. Of those who recovered one-half did so within one month, the other one-half within two to six months. Sixteen patients (24 per cent) had achieved normal renal function and were free from granular casts by the time they were evacuated. However, residual albuminuria, usually with slight microscopic hematuria, was still present. The remaining forty-one patients (62 per cent) were considered probable candidates for chronic nephritis. All had persistent granular casts and raised E.S.R.; renal function was impaired in thirty-two. Details are given in Table v.

A follow-up study is being carried out. So far, subsequent progress has been reported in twelve patients. Of five evacuated as probably chronic cases, two were much the same six months later but three had improved; of seven evacuated with residual albuminuria, with or without red cells in the urine, three recovered within six months and four were much the same.

The unfavorable outlook in this series, however, does not reflect the true prognosis of acute nephritis in this group for these patients were investigated at a base hospital and many were transferred to it because they were severely ill or did not recover quickly. Reports on prognosis from forward hospitals appeared more favorable.

There was no substantial difference in age between those who recovered while under observation and those who were evacuated with persisting signs of renal disease. Contrary to the opinion of Fishberg[3] the degree of hypertension was less important than its duration; very high pressures were observed in some who recovered or who had nearly

recovered when evacuated; when hypertension lasted more than a month, however, the subject rarely did well. (Fig. 6.) The duration rather than the degree of early edema had a similar significance.

TREATMENT

While it is doubtful whether any treatment administered had any influence on the final outcome of the disease, certain transient effects were observed which have a direct bearing on pathogenesis.

Period of Absolute Starvation. As soon as the diagnosis was established the patient was put to bed on absolute rest and all food and fluid were withheld for forty-eight to sixty hours routinely. This measure appeared to initiate diuresis, reduction of edema and subsidence of hypertension. A similar but less pronounced and less constant effect resulted from rest alone without the rigid dietetic restriction. Simultaneously, the glomerular filtration rate rose sharply in some patients to average or high normal levels during the fast but returned to its previous figure soon afterward. This behavior is opposite to that of normal controls under similar fasting conditions when filtration drops markedly and therefore indicates temporary relief from glomerular block. An effect so transient and sudden as this suggests that in cases in which it occurred acute glomerular block is due to vascular spasm rather than to structural change. Otherwise it is doubtful if any material benefit resulted from dietetic restrictions. Moderate reduction of protein and fluid had little demonstrable effect nor did an increase influence the course adversely.

Bed Rest. During the acute phase of the disease bed rest appeared to be essential only as long as edema and hypertension were present. After these have disappeared we have often seen proteinuria and the number of red cells in the urine increase in patients in whom the E.S.R. was still accelerated. In two of these patients granular casts reappeared and in three concentrating power deteriorated. There is no evidence, however, that this means aggravation of the disease.

Penicillin. Moncrieff[15] and Suchecki[16] suggested that penicillin was beneficial in the treatment of early acute glomerulonephritis by eradicating responsible foci of infection. Although a diligent search for persistent foci of infection was made in all patients in this series and few were found, it was decided to give penicillin a trial in order to test the truth of the general belief that such foci play some part in determining the course of the disease. Twelve patients were selected for this purpose. They had been ill for four to twelve weeks and their

TABLE V

STATE OF PATIENT WHEN DISCHARGED OR EVACUATED

Result	Time in Months						Total	Per cent
	1	2	3	4	5	6		
Cured	4	1	1	1	..	1	8	12.1
Residual proteinuria; sedimentation rate normal	..	..	4	2	6	4	16	24.2
Proteinuria; sedimentation rate abnormal; renal function good	..	..	..	3	1	2	6	9.1
Nephritic urine; renal function impaired	1	2	3	7	12	4	29	43.9
Nephritic urine; renal function good; edema	..	..	..	1	..	1	2	
Nephritic urine; renal function impaired; edema	..	..	1	..	..	..	1	
Nephritic urine; renal function good; hypertension	..	1	..	..	..	..	1	
Nephritic urine; renal function impaired; hypertension	..	..	..	1	1	..	2	
Nephritic urine; renal function impaired; edema; hypertension								
Edema only								
Hypertension only	..	..	..	..	..	1	1	

condition was relatively fixed. Penicillin was administered intramuscularly in doses of 15,000 units every three hours to a total of 700,000 to 900,000 units. The only demonstrable effect was further acceleration of the E.S.R. at the completion of the course. The reason for this was not clear.

COMMENTS

Analysis of the data available from this group of patients with acute glomerulonephritis makes it possible to speculate on the pathogenesis of the disease.

The disease is obviously related to a previous infection, not necessarily streptococcal, the incidence of which in our series was almost identical with that of Longcope.[14] The interval of 16.5 days between the beginning of the infection and the first evidence of the disease is about a week longer than that in serum sickness, but our observation on the patient with vascular nevus suggested that the true interval might well be a week shorter; it resembles the interval which separates rheumatic fever and allied disorders from the preceding infection. The occurrence of rheumatic fever, Schoenlein-Henoch purpura and urticaria in about 10 per cent of our patients indicates that the etiologic factors in all these diseases may be similar. These conditions occurred infrequently alone among our hospital admissions, which makes this suggestion still more probable. An allergic basis is currently thought to be responsible for the latter diseases and experimental evidence in favor of an allergic origin for acute glomerulonephritis is steadily increasing.[17–20]

The morphologic substrate of an allergic reaction consists of a capillary lesion[21] and smooth muscle spasm.[22] The first manifestations of acute glomerulonephritis, occurring usually when the previous infection has subsided, appear to be the result of a widespread capillary lesion and arteriolar spasm. Glomerular obstruction, hypertension and edema usually occur simultaneously, yet we believe we have demonstrated that these are independent of each other and each has its own mechanism of origin. The evidence in favor of a generalized vascular reaction, independent of the renal process, is extensive. There can be no doubt, for example, that early edema does not depend upon renal insufficiency; thus it may precede all other evidence of nephritis by several days, as has been pointed out by Henoch,[23] Nonnenbruch,[24] Volhard[25] and others and it may occur, as in the cases of Guggenheimer[26] and in Case 18 of this series, without any renal involvement whatever; proof suggesting its dependency upon a capillary change was provided by the behavior of our patient with vascular nevus. Again, transient hypertension may occur without demonstrable renal involvement as shown in Case 18, and Pickering[27] has concluded that it is probably not renal in origin. He found that it behaved differently from the hypertension of chronic nephritis and did not appear to depend upon humoral mechanisms but upon a neurogenic one. While we do not question the importance of the renal element in the origin of hypertension of late renal disease, it is still unsettled what role it plays in the acute phase.

The glomerular capillaries are, of course, usually the site of severe morphologic changes, similar to those produced by Froehlich[21] in the capillaries of a frog mesentery. However, we have drawn attention to the fact that sometimes under the influence of complete starvation and thirst diminished glomerular activity may suddenly be reversed, to reappear with cessation of the starvation period. We think that this phenomenon can be explained if we assume that in addition to the morphologic component there is also spasm of the afferent arteriole which can be reversibly influenced through some dietary mechanism not yet clearly understood. If a sufficient number of glomeruli are thrown out of action, filtration is seriously reduced and retention of non-protein nitrogen follows.[28] Albuminuria is due to increased capillary permeability and hematuria provides gross evidence of capillary damage and may be the renal counterpart of petechiae in the ocular

fundus and skin. In view of the frequency of hematuria the rarity of systemic petechiae requires some explanation. Perhaps the discrepancy depends on the fact that the glomerular capillary pressure is greater than the pressure in the systemic capillaries. The renal tubules are necessarily affected by the vascular lesion involving the tufts and they may be further handicapped by vascular alterations in the afferent arterioles and tubular capillaries.

This hypothesis provides an acceptable explanation for the early manifestations of acute glomerulonephritis and makes understandable the occurrence of various clinical types and the independent behavior of the clinical manifestations. When systemic vessels are chiefly involved, hypertension and edema overshadow glomerular and tubular dysfunction or may even occur alone; if arteriolar spasm is more pronounced than increased capillary permeability, hypertension overshadows edema and vice versa. On the other hand, when the renal vessels are chiefly involved, hypertension and edema are less pronounced than renal lesions or may be absent altogether; if spasm of the afferent arterioles dominates the disorder, acute diminution of glomerular activity with impaired filtration and retention of non-protein nitrogen dominates the clinical picture; if spasm is less pronounced than simple damage of the capillary wall, hematuria and albuminuria are more conspicuous. It is not to be expected that conditions causing acute diminution of glomerular activity would not also profoundly alter the behavior of the glomerular capillaries and renal tubules so that reduced filtration with retention of non-protein nitrogen could hardly occur without hematuria, albuminuria, impaired concentration and cylindruria. On the other hand, damage to the glomerular capillaries could well occur without reducing filtration and without interfering with tubular function.

The hypothesis is adequate to account for the initial or acute stage of the illness. In the section dealing with the course of the disease we have shown that this stage lasts usually less than a month. Its end is marked by disappearance of edema, subsidence of hypertension and signs of diminished glomerular activity and in the most favorable cases also by disappearance from the urine of those abnormal elements indicative of a lesion of the glomerular capillaries. In the majority of patients, however, recession of some of the renal manifestations, namely, of albuminuria, microscopic hematuria and of the impaired concentrating power, is less prompt and these signs may be indicative of a subacute or chronic course. The idea that a persistent focus of infection is responsible for perpetuating an allergic renal reaction[8] is hardly tenable, except in isolated instances, because the manifestations which are most likely to be allergic are those which are not so perpetuated; again, persistent foci of infection are rarely found in those cases and penicillin in no way influences their course.

The question at issue is whether the allergic process behaves differently in the kidneys than in other tissues, or whether it subsides as elsewhere but, owing to peculiar conditions, leaves changes in the kidneys which tend to be irreversible. The enclosure of the swollen organ in the tough, unyielding capsule might be one of the reasons why the acute process leaves greater residual damage in the kidneys than in other tissues. It should be borne in mind that the pressure in the glomerular capillaries is much higher than capillary pressure elsewhere and consequently a slight residual impairment of the capillary wall, which in other parts of the body could not be detected, may manifest itself in the kidneys by albuminuria and hematuria. Our cases of the nephrotic syndrome, which developed without a gap from the acute stage, suggest that a chronic capillary lesion due to some undetermined mechanism may be the underlying fault. This possibility would avoid the necessity of invoking a dual origin of edema, continuing without interruption in the same patient.

The comprehension of a persisting tubular lesion which, according to the hypothesis

previously stated, is regarded as secondary to vascular events and might be expected to clear up soon after the renal vessels regain their normal function is more difficult. We have observed, however, several cases of sulfonamide obstruction of both ureters lasting for twelve to twenty-four hours, in which all symptoms and signs quickly subsided after removal of the obstruction by ureteral catheterization, with the exception of impaired power to concentrate urine which persisted for three to eight weeks. It seems, therefore, that the renal osmotic function not only can suffer very easily but once disturbed requires considerable time under ideal conditions to recover. Yet conditions in a convalescent from acute nephritis often are not ideal; as was pointed out in connection with the endogenous creatinine clearance, glomerular filtration often remains in this stage on the low side of the normal and its variations tend to disappear, suggesting a residual restriction of the glomerular surface.

The hypothesis then accounts for all the features and varieties of the syndrome if it is admitted that under certain circumstances an allergic lesion can produce changes which may persist. The concept of an allergic lesion which persists or even progresses long after subsidence of the acute infection which initiated it is not a new one. Subacute and chronic polyarthritis, initiated by streptococcal, gonococcal, dysenteric or other acute infection is believed by some to represent similar allergic behavior; indeed there is reason to suppose that the problem of chronic nephritis and that of chronic polyarthritis may be related. Many varieties of allergic dermatitis persist long after all traces of the provocative allergens have been removed from the system, while in some cases another factor is known to be responsible for perpetuating the disorder, for example, sunlight in sulfonamide dermatitis.

SUMMARY AND CONCLUSIONS

1. A clinical study of sixty-six patients with acute glomerulonephritis is presented; the average period of observation was 123 days.

2. The course was divided into two distinct phases: The first rarely lasted more than a month, the fully developed picture consisting of hypertension, edema, acute diminution of glomerular activity with retention of non-protein nitrogen and a rapid E.S.R., hematuria and albuminuria, accompanied by impaired concentration and the appearance of casts. The second showed a pronounced tendency to chronicity and was characterized by the absence of hypertension, edema or retention of non-protein nitrogen, but by the persistence of albuminuria, microscopic hematuria, impaired concentration, cylindruria, slight or moderate acceleration of the E.S.R. and also some restriction of the normal fluctuations of glomerular filtration.

3. The occurrence of partial syndromes suggested that the term acute glomerulonephritis is a misnomer; thus there were patients with transient hypertension and edema with little or no evidence of renal involvement; others with no extrarenal manifestations but with reduced filtration, hematuria, albuminuria, impaired concentration and granular casts and others with edema and albuminuria only, or associated with minimal red cells in the urine or with slight impairment of concentration (the nephrotic syndrome). The great majority were mixtures in varying proportions of these three types.

4. The hypothesis that the syndrome called acute glomerulonephritis is a generalized vascular reaction of the allergic type to streptococcal and probably other infections is discussed. In this view transient hypertension and edema are regarded as extrarenal manifestations due to general arteriolar spasm and to increased capillary permeability, respectively. Their respective renal equivalents appear to be acute diminution of glomerular activity with retention of non-protein nitrogen due to gross spasm of the afferent arterioles, as well as swelling of the glomerular endothelial cells and exudation in Bowman's space and pro-

teinuria. The chronic proteinuria, and possibly chronic edema in some cases, developing without interruption from the acute stage are believed to represent persistence of the capillary lesion.

5. A forty-eight-hour period of complete food and fluid starvation appeared to exert a transient beneficial effect on hypertension, edema and glomerular activity. Penicillin in no way appeared to alter the course of the disease.

6. When hypertension and edema lasted for more than one month, irrespective of their degree, the subsequent course of the illness was nearly always prolonged, which suggests that a certain number of patients in this series subsequently progressed into the chronic phase of the disease.

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Pulmonary Adenomatosis*

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PULMONARY adenomatosis, or infectious adenomatosis, is a rare, chronic, irreversible condition consisting of hyperplasia and metaplasia of the alveolar epithelium into tall columnar mucus-producing glandular tissue. Histologically it is benign but involves both lungs, eventuating in complete loss of respiratory function and death by asphyxia. Clinically its onset may start with an acute respiratory infection which never clears completely. Its course is marked by frequent superimposed pulmonary infections for which antibiotics only temporarily relieve the respiratory embarrassment and increase the vital capacity. It has been noted only in adults, with the possible exception of the case of a seventeen year old girl reported by Geever, Carter, Neuberger and Schmidt.[13] The disease has been found in Germany, China, Canada and the United States, cases being discovered with increasing frequency. The etiology has been undetermined but is believed by many to be a virus infection.

A similar disease in animals, chiefly in sheep, was first reported in 1891 by Eber, in Germany, according to Sims.[24] Bonne[3] states that Roux, in 1903 in France, described these lesions in sheep suffering from sheep pox and that Spronck discovered similar lesions in guinea pigs in 1907. Richardson[21] and Bell[2] give Helly credit for describing the first human case of pulmonary adenomatosis in Germany in 1907. His patient was a forty-three year old woman with "symptoms of tuberculosis." The following year Löhlein[21] recorded in the German literature an instance of a disease involving the right upper lobe and which was productive of a large amount of mucus. Adenomatosis of the lungs in mice, horses and rabbits has also been reported. In sheep in South Africa the disease is known as jaagsiekte.

Cowdry[5] and Cowdry and Marsh[6] described the disease as a specific endemic, chronic, catarrhal pneumonia which was fatal in two to eight months. They postulated that epithelial proliferation was secondary to thickening of the interalveolar tissue. There was little or no fever but marked respiratory distress, nasal discharge, cough, rales, weakness, weight loss and anemia. The gross and microscopic findings in sheep were identical with those found in humans. Dungal, cited by Bell[2] and Bonne,[3] described the disease in sheep in Iceland, proved its contagiousness and called it epizootic adenomatosis. It is probably similar to verminous pneumonia and Montana progressive sheep pneumonia. M'Fadyean,[3] Bonne,[3] Theiler,[3] Straub,[21] DeKock,[3] Richardson[21] and Geever et al.,[10] who reviewed the studies of Bosc, Borrel, Thorp, Hallman, Davis, Robertson, Osenkop and Furth, also reported the disease occurring naturally in animals. More recently Norris[19] found the disease in a guinea pig inoculated with pleural fluid from a patient convalescing from pneumonia. The patient had no evidence of the disease and this was thought to be a spontaneous occurrence.

The pathogenesis of abnormal pulmonary alveolar lining has been the subject of a great deal of controversy. We may consider the problem from several different aspects: (1) failure of normal development, (2) stimuli which excite abnormal proliferation and (3) experimental production of abnormal alveolar epithelium. Normal alveoli in early fetal life appear glandular and

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are lined by a cuboidal epithelium thought by most investigators to be of entodermal origin, according to Maximow and Bloom.[16] In the human embryo of 170 mm. the continuous epithelium becomes interrupted by blood vessels, eventually leaving the epithelium as isolated round cells and the capillary walls exposed to air. Zeldes[31] has shown that during the twenty-fourth to thirty-third week of intra-uterine life the transition to the adult type of alveolar lining occurs. The mechanism of this transition is said to be by a disintegration of nuclei, degeneration of cytoplasm and casting-off of the cells or by encroachment of capillaries and desquamation of the epithelium. Persistence of the large cuboidal cells, Zeldes demonstrated, is not compatible with respiration and therefore with life and has been found to be persistent in 50 per cent of "viable" premature infants and in 20 per cent of full-term infants. Reviewing our autopsies of premature and full-term infants with "failure of lung expansion," we found persistence of cuboidal epithelium frequently and aspiration of amniotic fluid and cells as the other common cause; occasionally we found the two together.

The work of el Gazayerli[9] and others rather conclusively demonstrates the origin of the alveolar phagocyte which is of importance because of the association of phagocytes with adenomatosis and the infrequent mitotic figures seen in these instances. These observers demonstrated that the cuboidal cells which are located in the angles of the alveolar spaces give rise by mitosis to the free alveolar phagocytes. By injection of trypan blue these cells have been shown to phagocytize the dye, as do other cells of the reticulo-endothelial system, while the other flattened polygonal alveolar epithelial cells do not.

In the fully developed lung certain stimuli have been found which excite abnormal proliferation, hyperplasia and metaplasia. The excellent descriptions of Bell[2] and of Geever et al.[10] include: (1) chronic passive congestion associated with old mitral or aortic valve disease, (2) infectious diseases of the lungs, particularly when a chronic interstitial pneumonia results, (3) lung adjacent to nodules of chronic granulomas, tuberculosis, silicosis, syphilis and to (4) old empyema pockets, (5) old pleuritic adhesions, (6) chemical pneumonia, (7) lipoid pneumonia, (8) other aspiration pneumonias, (9) war gases such as phosgene, (10) physical agents such as x-rays and radium, (11) lung adjacent to benign and malignant neoplasms and (12) toxoplasmosis. Chronic anoxia, with loss of alveolar function due to thickening of the interalveolar septa or to filling of alveoli with foreign material, appears to be the basic cause of the disturbance. It has been suggested that bronchial epithelium grows down into the alveoli, but numerous transition stages indicate that the epithelium develops from cells already present. A vicious cycle is set up, with the thickening of the alveolar septa and viscid mucus preventing oxygen from reaching the capillaries and stimulating alveolar epithelization with cuboidal to mucus-producing columnar cells.

Similar changes in alveolar epithelium have been produced experimentally. Young[30] produced diffuse epithelial proliferation in the lungs of rabbits consistently with optimum concentrations of various electrolytes. The alkali metals, Li, Na and K and the alkaline earth metals Mg, Ca and Sr, were found effective only in strong solutions. The trivalent metals, Al, La and Fe, were efficient, and the heavy metals were effective in weak solutions, the order of their efficiency being Hg, Ag, Cu, Cd, Pb and Zn. Grady and Stewart[14] induced pulmonary tumors of this nature in strain A mice, using subcutaneous injections of 1,2,5,6-dibenzanthracene or methylcholanthrene in lard suspensions and using lard as controls. Five weeks after injection tumors began to appear, practically all growths of alveolar origin and not associated with inflammatory reaction. In many instances there was no distortion of pulmonary architecture, alveolar lumens remaining

TABLE 1

PULMONARY ADENOMATOSIS

Observer	Year	Age	Sex	Nationality	Symptoms	Duration	Urine	Blood	Mitoses	Invasion	Description of Lung
1. Helly	1907	43	F	German	Symptoms of tuberculosis						
2. Lohlein	1908	..	..	German	Abundant mucus	.....	....	.....	.....	.....	Right upper lobe
3. Bonne	1939	31	M	Chinese	Fever, persistent cough, mucus, dyspnea, emaciation	9 mo.	Negative	Negative	Fairly numerous	Yes, no metastases	Weight 2,700 Gm., bilateral disease; moist, pale, friable tumor nodules
4. Richardson	1940	73	F	American	No symptoms of lung disease; died of obstructive jaundice; stone in common duct	.....	Bilirubin	.....	.....	.....	Small, firm, scattered nodules, 2–10 mm., bilateral all lobes
5. Taft and Nickerson	1941	62	M	American	Pleurisy, cough, fatigue, mucus sputum, weight loss; dyspnea, cyanosis, fever; tuberculin test slightly positive	8 mo.	....	White blood cells elevated	.....	.....	Weight 700 and 850 Gm.; several small areas of cavitation 0.4 to 1.5 cm.
6. Taft and Nickerson	1943	79	F	American	Pernicious anemia in relapse, increasing pulmonary infections; diverticulosis, cholelithiasis	.....	....	Type VIII pneumococcus; hemolytic staphylococcus	.....	.....	Weight 420 and 700 Gm. bilateral disease
7. Bell	1943	63	M	American	Dyspnea, cough, weakness, weight loss, mucus sputum	2 yr.	Negative	Negative	.....	.....	Heavy lungs, firm, solid homogeneous tumors
8. Sims	1943	42	M	American	Dry cough early, then mucus sputum; pain, weakness, fever, cyanosis, clubbed fingers	2 yr.	....	White blood cells elevated later 3,700	Occasional		
9. Oberndorfer	1930	21	..	.....	Septic hemorrhagic pneumonia	.....	....	.....	.....	.....	Bilateral, dark red, one apex free
10. Wood and Pierson	1942	57	F	American	Fatigue, night sweats, cough; developed carcinoma of cervix after lobectomy	2½ yr.	Negative	Negative	Infrequent	None	2.0 cm. cavity, 0.1 cm. nodules; one lobe removed surgically
11. Alexander and Chu	1947	56	F	American	Fever, pleuritic pain, cough, sputum, dyspnea, cyanosis	5½ yr.	Albumin, red blood cells	Hb. 11; positive Wassermann	None	None	Weight 2,100 Gm.; necrosis resembled Friedländer's infection, green, gelatinous; also had pancreatic island adenoma
12. Reinhart (O.S.U.)	1946	This patient was seen by us, but the case has not been reported							.....	.....	Voluminous lungs, bilateral disease
13. Paul and Ritchie	1943	68	F	American	Severe dyspnea for 6 mo., cough, small amount frothy sputum, weight loss, cyanosis	6–8 yr.	....	White blood cells 32,400	?	Yes	Extensive pneumonia bronchiectatic cavities, largest 7 cm.
14. Paul and Ritchie	1945	52	M	American	Increasing dyspnea, weight loss, cyanosis	2½ yr.	....	.....	.....	.....	Left lung granular, nodular, bronchiectasis; acute and organic pneumonia ? more active, ? malignant
15. Paul and Ritchie	1943	60	F	American	No pulmonary complaints; carcinoma of pancreas; metastases to liver, gallbladder	.....	....	.....	.....	.....	Bronchiectasis, atelectasis, emphysema, acute and organic pneumonia, one local area with obvious benign proliferation of bronchial epithelium
16. Paul and Ritchie	Unpublished, similar										
17. Simon	1945	70	F	Canadian	Cough, thick white mucus. Dyspnea, orthopnea, cyanosis, emaciation	7 wk.	....	.....	0	0	Obliteration of right thorax, dense adhesions; band of consolidation, elevation, granular, sticky, all lobes
18. Simon	Unpublished, but similar										
19. Geever et al.	1943	17	F	American	Cough, fever, weight loss, dyspnea, cyanosis	13 mo.	....	.....	Rare	.....	Obliteration of pleural cavity, diffuse gray nodular tumors, pinhead to 1 cm. size, columnar mucus product, occasional pseudostratified and papillar proliferation
20. Fidler, Erwin and Bubis	1946	66	M	American	Chest pain, severe to moderate cough, yellow mucus sputum, cyanosis	Moderate cough for several yr.	....	White blood cells 20,300	Few	None	1,370 Gm. each, firm, pale solid nodules
21. Fidler, Erwin and Bubis	1946	63	M	American	Same as above, plus severe emaciation and weakness	.....	....	White blood cells 18,000 slight anemia	.....	.....	Same as above

patent and the walls lined by cuboidal cells producing a glandular appearance. There was no connection of these tumors with bronchi. There were some solid nodules of tumor tissue and a few mitotic figures but no evidence of malignancy. Geever et al.[10] report that Wells, Slye, McDonald and Woodhouse, Holmes, Andervont, Breedis, Robertson, Osenkop and Furth produced similar lesions with tar as did Simonds and Curtis.[23] Bell[2] states that Grumbach found glandular epithelium developing in guinea pigs with experimentally produced pneumonia.

There is some support for the suggestion of Cowdry and Marsh[6] that pulmonary adenomatosis is incited by a virus. Straub[25] found adenomatosis in mice infected with influenza virus. Bonne[2] states that Theiler thought the disease in horses was due to a poisonous plant, *Crotolaria dura*. Dungal reported associated nematodes in the lungs of sheep, and DeKock thought it a neoplasm found in sheep. Many others believe it a neoplasm and describe similar cases, differing only in that they found regional, brain and bone metastases. However, Taft and Nickerson[27] conclude in reporting their two cases that "this condition is of but little significance in the genesis of pulmonary carcinoma in general."

We are presenting two cases of patients with benign pulmonary adenomatosis autopsied at the White Cross Hospital, Columbus, Ohio, in 1946. Nineteen cases have been found in the literature to date. The ages range from seventeen to seventy-nine. Geographical distribution and occupation varied widely. No contact with any infected animal was recorded. Most of the patients had in common a prolonged history of at least eight months' duration, apparently following an acute pulmonary infection which did not clear up entirely. The blood and urinary findings were usually normal. Fever, malaise and leukocytosis when present were remittent in character depending upon secondary infections. Cough productive of copious mucoid sputum was almost universal. The sputum was negative for acid-fast organisms or any other constant invader and the tuberculin test when done was negative or only slightly positive. Weight loss, weakness, severe dyspnea and cyanosis were also present. In only one case was clubbing of the fingers described. Although there was chronic lung disease over long periods, cor pulmonale was not noted. Two patients had no symptoms of lung disease at all, one case reported by Richardson[21] and one by Paul and Ritchie.[20] The immediate cause of death was anoxia or sepsis from acute pulmonary infection except in Richardson's patients who died of obstructive jaundice due to a stone in the common duct, Wood and Pierson's[29] patient who died of metastatic adeno-acanthoma of the cervix and one of Paul and Ritchie's patients who died of carcinoma of the pancreas with regional metastases. One of Taft and Nickerson's[27] patients also suffered from pernicious anemia in relapse, associated with increasing pulmonary infection and bacteremia. The gross and microscopic pictures were all similar, with the possible exception of those of Paul and Ritchie,[20] one of Geever, Carter, Neuberger and Schmidt[13] (who emphasized the radiologic findings and only briefly described the gross and microscopic findings) and one case of Simon[22] which has not yet been reported but is said to be similar.

Pulmonary lesions similar to those of infectious adenomatosis but with metastatic lesions have been reported by Sweany,[21] recording cases of Wolf, Kretchmer, Pépère, Morelli, Perls, Fuchs, Tillman, Grunwald, Briese, Domeny, Oberdorfer, Knierim, Saltykow, Ribbert, Chiasi, recorded by Bonne[3] and by Kaufman, Letulle, Weisman, Rous, Frissell and Knox in the paper by Neuberger.[18] Most metastases were to regional lymph nodes but occasional sites were found in the bones, liver and brain. Cassilli and White, according to Neuberger,[18] reported a case which they named "carcinomatoides alveogenica multicentrica," in which the lesion was confined to the lung sacs and did not invade the septa or bronchi nor did it metastasize. Geever, Neuberger and Davis[12]

listed five cases which they believed were malignant. In neither of our cases was there invasion, metastasis or evidence of malignant change.

CASE REPORTS

CASE 1. A white male, sixty-six years old, was admitted to the medical service March 26, 1946, with the chief complaint of pain in his chest for three months. Three months prior to admission the patient had pneumonia from which he had never made a complete recovery. He had been ambulatory only for a brief period of one week. Since the onset of his illness, he had had intermittent fever without chills, a severe cough accompanied by the production of a yellowish mucous sputum and left chest pain which was aggravated by coughing. The past history revealed that he had never been entirely free from a cough for the past several years of his employment as a molder. Other complaints were non-contributory. On admission his temperature was 101.2°F., pulse rate 96, respiration 94 and blood pressure 125/88. Physical examination revealed a well developed, well nourished white male of stated age. The essential findings were those limited to the chest. There were accentuated breath sounds, with a friction rub and dullness to percussion in the lower portions of each lung. No other significant findings were reported.

Laboratory examination of the urine was negative; hemoglobin, 16 Gm.; red blood cells, 5,300,000; white blood cells, 20,200 with 88 per cent polymorphonuclear cells. Clinical impressions were silicosis, pneumonitis and possible lung abscess.

X-rays of the chest taken on March 7, 1946, revealed no apparent abnormalities of the heart and aorta; the upper third of each lung was clear. Mid- and basal linear markings were intensified bilaterally, with a considerable amount of pneumonitis in these areas. It was though that there were several small cystic areas in both bases, with the addition of a slight amount of left pleural fluid. On March 29, 1946, lipiodol instillation indicated a saccular bronchiectasis in the basal portion of each lung, more marked on the right and anteriorly.

Sulfadiazine therapy was started but was later changed to penicillin; there was a resultant drop in temperature to 97.2°F. within twenty-four hours. The temperature remained at normal levels for three days, during which time penicillin was continued. Because of a rise in temperature at the end of this period, sulfadiazine therapy was given again. There was a temporary response but on the eighth hospital day the patient became progressively worse, semicomatose and had to be restrained. Respirations were harsh and labored and the pulse feeble. Death occurred as the temperature rose to 104.6°F.

When the chest was opened at autopsy, both lungs were found to meet in the midline anteriorly and to completely obscure the cardiac area. The lungs were bound to the chest wall by old, dense, pleural adhesions which could be separated only with difficulty. The left lung weighed 1,370 Gm. The upper lobe was partly crepitant while the lower lobe was denser and mottled. Upon dissection of the tracheobronchial tree the left bronchus was found to be slightly narrowed in its lower division and contained a slight amount of thin whitish exudate. The cut surface showed a diffuse anthracosis and no cavities. The lower lobe showed a mottled greyish-yellow consolidation about which the deeply anthracotic lung slightly retracted, causing these areas to appear elevated above the cut surface. Again, a thin, purulent fluid could be expressed. The lung contained no evidence of malignancy or tuberculosis. A few similar scattered, shot-like areas appeared throughout the upper lobe. The right lung was similar to the left except that its bronchial tree showed no evidence of atelectasis and the upper lobe contained only a few small areas of inflammatory reaction. The middle and lower lobes were largely fused by pleural adhesions and their cut surfaces were also extensively mottled and grossly similar to the other lobes. The peribronchial and hilar lymph nodes were quite hard, elastic and of a deep black color.

Microscopic sections from the right and left lungs showed an entirely similar picture, consisting of chronic congestion and moderate anthracosis throughout the upper lobes, with small areas of inflammatory reaction similar to that found diffusely throughout the lower lobes. In these lobes there was a process quite similar to a partially organized pneumonia in which the alveoli were filled with a fibrinopurulent exudate but showed only slight fibrinous organization with a subacute exudate filling the alveoli. The alveolar lining cells showed a process of proliferation and metaplasia producing a benign adenomatosis in which some

alveoli were lined by hyperplastic cells while others were widened and distended with a mucous secretion. The cells lining such alveoli tended to a columnar form, sometimes showing a globular secretion. This process could be traced from alveoli in which no such reaction was present, except for the presence of some pneumonic exudate, through those in which there was slight to moderate alveolar epithelial hyperplasia, to those just described in which the alveoli varied from solid to cystic. In such cystic areas the exudative reaction largely disappeared. The process was that of adenomatosis. There was no evidence of tuberculosis or silicosis. The pleurae showed a marked chronic fibrous thickening. The hilar lymph nodes showed no recent inflammatory reaction but were replaced by a sclerotic type of fibrosis, together with anthracosis and slight calcification.

Case II. A sixty-three year old white male was admitted to the medical service on October 9, 1946, with the chief complaint of coughing and shortness of breath for five years. These symptoms had gradually progressed, with recurrent bouts of coughing and fever which were largely relieved by intensive chemotherapy but which would recur when such treatment was discontinued. Dyspnea had increased during the past year without paroxysms and without orthopnea or pedal edema. The cough was relieved when the patient lay on his left side but was aggravated when lying on his back or right side. In August, 1946 repeated chest films, including lipiodol injection, showed a patchy opacity throughout the lower three-fourths of the right lung and in the mid-portion of the left lung there were numerous patchy nodular areas accompanied by increased bronchial markings. The process was thought to be of granulomatous character. Repeated examination of the moderate amounts of sputum which were being produced at that time revealed a number of Friedländer's bacilli and a few diphtheroids but no fungi could be demonstrated on direct smear or culture.

Upon admission the blood showed hemoglobin, 10 Gm.; red blood cells, 3,500,000; white blood cells, 18,000 with 90 per cent polymorphonuclear neutrophiles. The temperature was 100.2°F., pulse 84, respirations 20 and blood pressure 110/70. Physical examination revealed a weak, emaciated, moderately cyanotic white male. Examination of the chest disclosed marked dullness at the right base extending up to the fourth rib posteriorly. Breath sounds were normal except over this area where they were of marked bronchial character. The whispered voice was clearly transmitted over this area and fine and coarse rales were heard above this region. The heart was thought to be slightly enlarged to the left.

X-rays of the chest showed a patchy opacity throughout the lower three-fourths of the right lung and a large area of consolidation in the mid-portion of the left, with apparently many fibrous strands along the line of the bronchial trunks in the lower half of the left lung. The radiologist's impression was that the process was a granulomatous one probably caused by a fungus.

After admission there was an elevation of the temperature to 103°F. With the use of chemotherapy, this was brought down to normal levels; however, dyspnea increased and the patient expired on the eighth hospital day.

Autopsy findings disclosed both lungs to be voluminous, almost meeting in the midline beneath the sternum. The left lung was bound by old, dense adhesions over the posterior and lateral aspects to the thoracic wall. The right lung was firmly fixed, the adhesions being especially dense over the lower lobe and medial surface. The lung weighed 1,325 Gm. The entire lung was discolored except for a small amount of aerated marginal tissue on the lateral side of the upper lobe. The surface was elevated and nodular, other nodules being palpable within the substance of the organ. Dissection of the bronchial tree showed no evidence of malignancy or obstruction. Cut surface of the lung revealed extensive mottling of the studded surface, these markings being prominent throughout the central portion of the lung and the major portion of the upper lobe. These masses were confluent, presented a granular, carcinomatous-appearing surface and adjacent areas were more discrete but also presented a hard grayish carcinomatous appearance.

The right lung was similar in its upper and middle lobes. These lobes were fused and largely replaced by tissue similar to that found on the opposite side. The lower lobe was small and completely atelectatic. The bronchial tree on this side was free from gross obstruction or malignancy; there was no enlargement or apparent involvement of the mediastinal lymph nodes by this process.

Microscopic examination of the lungs showed

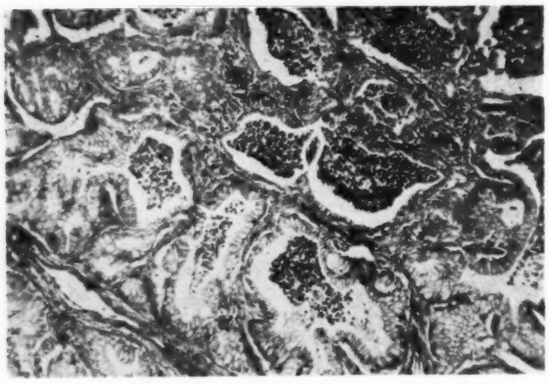

FIG. 1. Case No. 1456. Here can be seen a transition from a flattened alveolar epithelium to cuboidal and columnar mucus-producing glandular epithelium. The septa are thickened and the dilated alveoli are filled with mucopurulent exudate; low power.

a similar picture in each, consisting of a hyperplastic overgrowth of alveolar epithelium with a high columnar type in which the cytoplasm was clear with occasional mucoid, mucus frequently filling the distended alveoli. (Fig. 1.) This process was circumscribed into nodular areas by moderate interstitial fibrosis and in the uninvolved areas there was frequently pneumonic consolidation. There was no evidence of malignancy.

COMMENTS

A brief comparison of several points common to both of these cases may help to emphasize some of the salient features of this disease. Onset was in the latter decades, with cough, dyspnea and production of sputum. Although x-ray films of the chest in each patient pointed to pneumonitis, probably of a granulomatous type, they were not diagnostic. Specific etiologic organisms were not identified. Further routine laboratory procedures failed to be of value and examination of the urine and blood was negative.

The clinical courses were somewhat parallel—a long gradual downhill trend accompanied pulmonary symptoms, with occasional exacerbations. There was even more striking similarity pathologically; in each case there was the massive increase in the size and weight of the lungs. Dense adhesions fixed the lungs to the thorax; there was nodular consolidation throughout and a variegated, mottled cut surface. Microscopically a particular pattern was observed. In or near the nodular areas was found a net-like arrangement, the stroma of which consisted of normal alveolar septa with variable increase in amounts of supporting tissue. This fibrosis was apparently the result of previous secondary infection and major increases were noticeable in older areas of the disease process as indicated by x-ray findings. The septa were lined by very tall columnar, mucus-producing, non-ciliated cells with oval or round, basal, vesicular nuclei. Larger areas of normal lung tissue were definitely separated from areas previously described by thickened alveolar septa, compressed or atelectatic lung and other areas of minimal alveolar lining hyperplasia and metaplasia. The presence of secondary infection influenced the picture. Grossly it added to the amount of exudate and to the mottled discoloration of the pleural and cut surfaces. The alveoli could be classified or divided according to the type and amount of exudate they contained. Some contained only a few phagocytic cells, others were heavily choked with a mucopurulent exudate while still a third group contained a large number of round phagocytic cells in a background of mucinous material in which no evidence of infection remained. Most of the bronchioles contained large amounts of mucopurulent material. None of these air passages showed any evidence of invasive destruction; most had thickened walls. In a number of sections there was inflammatory loosening and destruction of bronchiolar epithelium.

Only one microscopic difference between these two cases was apparent. In the first case there was a larger proportion of mitotic figures among the hyperplastic alveolar epithelial cells. Whether these represented activity of these epithelial cells themselves or of the reticulo-endothelial phagocytes could not be determined definitely. However, such figures were noted particularly in those cells which had been pushed well into the lumina of the alveoli and many if not all appeared to give rise to the round phagocytic cells

which were extruded well into the lumina of the alveoli after division.

Examination of seventy-six cases of pulmonary diseases from our slide library revealed varying amounts of pulmonary alveolar epithelial hypertrophy and hyperplasia, the lining cells attaining a low columnar pattern in two cases of bronchiectasis. In no cases were tall columnar cells found or any evidence of mucus production. Little or no variation from the normal morphologic pattern was found in the usual case of acute pulmonary disease, for instance in fetal pneumonia, acute passive congestion, acute bronchial and lobar pneumonia and early stages of infarction. Occasional cases of chronic passive congestion showed no change in the areas studied. No change was seen surrounding a Ghon complex and only slight hypertrophy and hyperplasia were noted in four of five patients with lung abscess. In cases of pulmonary tuberculosis much of the increase in size and number of alveolar lining cells appeared to be related to the increased number of alveolar phagocytes, but this was not generally true as numerous phagocytes were found in patients with acute passive congestion, lobar and bronchial pneumonia and lung abscess in which only slight or no hypertrophy or hyperplasia were found. The cuboidal alveolar epithelial cells could be differentiated readily in most cases from the phagocytes and their precursors.

These findings are similar to those of Bell[2] and others and suggest that a diminution in the oxygen supply to an area of the lung may be the stimulus for hypertrophy and hyperplasia of the alveolar epithelium. However, review of these cases gives no clue as to the pathogenesis of metaplasia to mucus-producing columnar cells.

SUMMARY

Within one year two cases of benign pulmonary adenomatosis were discovered at autopsy. This is a comparatively rare condition, only nineteen human cases having been recorded previously. However, almost all of them had histories and physical and x-ray findings which were similar. These findings should lead the observer to suspect the condition if they are seen again: (1) There is a long, slowly progressive downhill course, with pulmonary symptoms following an acute infection which never clears completely. (2) There are exacerbations with partial remission of symptoms due to the superimposed infections. (3) X-rays show a diffuse conglomerate pneumonic infiltration, with little change over a period of months or years. (4) To date sputum examinations have revealed no causative organism. (5) Grossly the lungs are voluminous, heavy, with raised, moist, gray patches of tumor. Microscopically there is a transformation of the normal alveolar lining by hyperplasia and metaplasia to a benign mucus-producing columnar epithelium.

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Chronic Pulmonary Granulomatosis

Report of Ten Cases

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In 1943 two of us first reported the occurrence in the United States of an acute pulmonary involvement occurring in workers extracting beryllium oxide.[1] A subsequent, more comprehensive report of acute manifestations in these same patients was published in 1945.[2] Since the initial publication, beryllium and its compounds have been under investigation as a possible source of both acute and chronic conditions in man although final convincing proof of a relationship is still lacking.

Industrial concerns employing and manufacturing beryllium and its compounds have not waited for conclusive evidence of beryllium toxicity but began at once to develop measures to decrease exposure of their workers to this element. The industry has also taken steps to reduce the amount of beryllium compounds escaping through its various exhausts into the surrounding atmosphere.

The syndrome under discussion is most commonly known as chronic pulmonary granulomatosis. It has been described by Hardy and Tabershaw[3] and by Higgins.[4] It has also been referred to as miliary sarcoidosis, chronic granulomatous pneumonitis, delayed chemical pneumonitis and beryllium sarcoid. The purpose of this report is to make available clinical, laboratory and roentgenographic data to aid in the early diagnosis and management of this chronic pulmonary disease.

It is noteworthy that since 1944 or 1945 exposure to beryllium has been much less frequent because of the steps taken by manufacturing plants. Consequently, in preparing this report we wish to point out that the majority of the case histories presented in this paper were of those who were exposed to beryllium compounds prior to 1946. Of the many who were exposed before 1946 only a small number have shown any symptoms.

ETIOLOGY AND PATHOLOGY

At present no etiologic factor or combination of factors has been definitely established as the cause of chronic pulmonary granulomatosis. Previously reported cases have been closely associated with the handling of phosphorus in the manufacture of fluorescent lamps.[5] In the series of cases presented four of the patients worked in a plant producing beryllium and four of the remaining six lived near the plant. However, consideration must also be given to agents other than beryllium such as infection, copper, manganese and zinc. On his last visit to Cleveland, Dr. L. U. Gardner suggested the possibility of a diphtheroid organism or other bacteria or viruses becoming virulent in the presence of certain chemical compounds. In spite of the failure to identify the cause with certainty, public health officials as well as industrial sanitary engineers have drawn attention to beryllium.

Because of lack of knowledge of the exact etiologic factors, little has been advanced theoretically as to the pathogenesis of the disease. On the theory that the etiologic agent is an insoluble organic or inorganic compound it is possible that phagocytes, in the usual response to irritants, engulf the minute particles of the compound in the finer bronchioles and respiratory alveoli. Some of the cells die locally owing to the toxicity of the agent with the characteristic tissue reaction of formation of sarcoid-like

nodules. Other cells are capable of migrating into the local lymphatic system and still others into the blood capillaries, a mechanism which would explain the nodular reaction.

HISTORY

Six of the ten persons reported had not worked with metallic beryllium or its compounds but four of them lived within a radius of 300 meters from a beryllium plant for periods of from one to four years. The fifth lived about three miles from the plant, where her husband was employed, but at no time did she handle his work clothing. Probability of direct exposure was questioned but denied. The sixth patient lived approximately one-half mile from the plant for about one year. She had no complaints nor did she manifest any respiratory difficulty while in this area. Her residence since has been two to three miles from the plant and her only possible contact during this time has been with a friend whose father was employed in a beryllium plant. The entire exhaust material from the plant has not been thoroughly investigated; however, preliminary samples in the proximity revealed minimal contamination with beryllium compounds for a short distance only.

All six of the patients hereby reported as out-plant cases were brunette women who ranged in age between twenty-two and thirty-five years. In five instances the disease had manifested itself from one to eight months postpartum. In the sixth instance the interval between delivery and onset of the disease was almost two years. Of the four remaining patients one worked in a beryllium plant for six weeks during the summer of 1941 and his earliest symptoms appeared while he was in the army in 1944. The second patient was employed in the laboratory of a beryllium plant for twelve weeks from November, 1943 to February 1944, and her first symptoms appeared in August, 1946. Neither had any manifestations of the acute form of the disease while working in the beryllium plant. The third patient worked in a beryllium plant for eight weeks in 1941. He left this employment after having developed a cough and shortness of breath which he attributed to chemical bronchitis. His first symptoms of chronic pulmonary granulomatosis appeared in January, 1946, and during the intervening years he had not been exposed to any other chemical or occupational hazards.

The fourth patient developed an acute chemical bronchitis in May, 1945. Upon complete recovery two months later he returned to work as a beryl ore grinder. Within ten days he again disclosed clinical symptoms and findings of acute bronchitis. After full recovery he was released from the industry in September, 1945 and has since avoided chemical contact.

Clinical and Roentgenographic Data. The clinical history was characteristic in all cases. The onset was rather insidious and because of the mildness of the process in the early months the patients failed to seek medical attention. The typical history was a mild productive or non-productive morning cough usually following an acute coryza. In a few months the cough became more pronounced and dry in character and sudden changes in air temperature and humidity sometimes elicited a severe attack of paroxysmal coughing. Substernal pain and discomfort were frequently noticed during the coughing attacks or upon attempted deep breathing.

Concomitant with the paroxysmal cough there was exertional dyspnea which became more pronounced as the disease progressed. Acrocyanosis, "watchglass" fingernails and clubbing of the finger tips were present in the later stages.

Physical examination in all patients revealed some weight loss, depending upon the stage of the disease. The vital capacity was diminished greatly, chest expansion was definitely limited and substernal pain was experienced at the height of inspiration. The percussion note was resonant throughout and fine, crackling rales were audible in the hilar areas in the advanced stages of the disease. Abdominal examination proved entirely negative in all except Case 1 during

the terminal months of the illness. No such skin or glandular lesions as were described by Higgins[4] have been observed.

Laboratory studies, including complete blood counts, Kline and Kahn tests, urinalysis, sedimentation rate, non-protein nitrogen and blood sugar determinations were within normal limits in all cases. Albumin globulin ratio was within normal limits in all cases.

Chest roentgenograms revealing a ground-glass appearance with minute nodules throughout the lungs is one of the outstanding characteristic diagnostic features of the disease. The small nodules are unquestionably the result of coalescing granules. The fact that symptomatic onset of the disease precedes positive roentgenographic findings by several months is verified in the histories of the reported cases. Roentgenograms of the hands in all living patients did not reveal any abnormalities.

Two of these patients died and autopsies were performed. Nodular lesions were confined to the lungs, hilar glands and the liver. The pathologist's reports are given in detail in connection with Cases I and II. Beryllium was not recovered from the tissues of one of the patients in whom an autopsy was performed; in the other quantitative studies were equivocal. Beryllium analysis of the urine revealed small amounts in two patients (Cases VI and VII) and none in the other two patients (Cases III and V).

Differential Diagnosis. There is need for great caution in making a specific roentgenologic diagnosis, especially on single plate observation. All other possibilities must be eliminated by exhaustive exposure investigation, by serial roentgenogram study, by clinical course pattern and by laboratory procedures. Furthermore, the possible coexistence of multiple etiologic factors must be given consideration. Differential diagnosis must include consideration of miliary tuberculosis, tuberculosilicosis, Boeck's sarcoid,[6,7] miliary carcinomatosis,[8] pneumoconiosis,[9,10] erythema nodosum,[11] coccidioidomycosis[12] and acute chemical pneumonitis.[12,13] Differential highlights have been given by Pascucci[14] in his recent report of similar cases.

Prognosis. The prognosis remains guarded. Most cases have been diagnosed in the later stages of the disease while only a few have been detected in an earlier phase. At the present time the first patient seen in consultation with Dr. L. U. Gardner in 1945 is living and while she has improved clinically, roentgenograms of the lungs remain unchanged. Three others (Cases VI, VII and VIII) have manifested clinical improvement in the last six months and are allowed minimal physical exertion.

Treatment. No specific treatment has been suggested up to the present. Since the cause or causes are not yet established, treatment is empirical. BAL (2,3 dimercaptopropanol) has been used without particular success. Aminophyllin, benadryl and cough sedation have been used symptomatically with some degree of relief. In two patients during attacks of chills, high fever, shortness of breath and severe acrocyanosis intravenous injection of 10 to 50 mg. of benadryl produced an amazing alleviation of symptoms immediately and a sudden drop in the temperature to normal, a condition which persisted for several days.

The most effective treatment at present depends upon early diagnosis and consists of prescribing minimal exertion so that the patient's physical reserve is not impaired. It has been observed that a clear, dry and warm environment is conducive to clinical improvement even though roentgenographic findings remain unchanged. Because of decreased vital capacity in these patients, great caution must be observed to avoid any acute respiratory infection.

CASE REPORTS*

CASE I. A white woman, who was thirty-eight years old at the time of her death on July 15, 1946, complained of a progressive respiratory difficulty of two and one-half years' duration. The apparent onset was in January,

* Clinical data furnished through the courtesy of Dr. M. E. Kishman, Dr. L. Hait, Dr. H. Marsico of Lorain, Ohio, and Dr. Russell Dickason of Vermilion, Ohio.

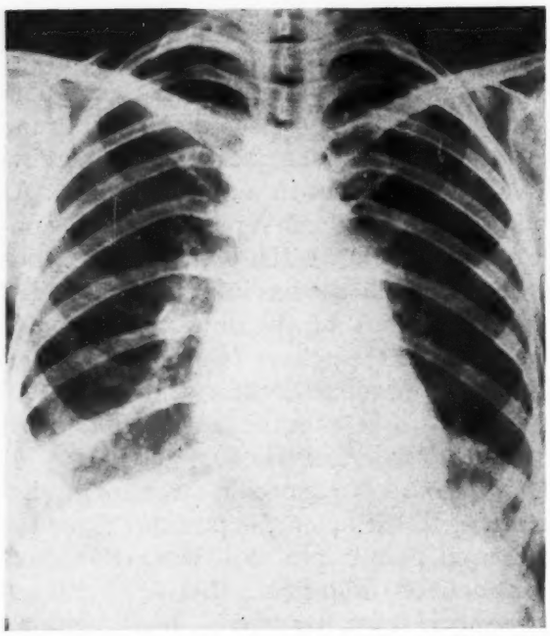


FIG. 1. Case 1. Fine diffuse granular infiltration throughout lung fields, with cardiac silhouette of secondary cor pulmonale; five months prior to death.

1944 when the patient suffered a cold after which she experienced persistent weakness, a slight but constant cough, dyspnea on exertion and a slight loss of weight. She did not have chills or fever. On April 13, 1945, she was delivered of her second child and on October 12th stated that she had lost over 20 pounds during the preceding summer. Her cough had become more pronounced and also spasmodic and while it had been productive during the summer was dry at the time of examination. She complained of severe dyspnea and of substernal pain on inspiration. Examination revealed acrocyanosis and slight clubbing of the fingers and toes. Expansion of the chest was diminished, but percussion and auscultation revealed no abnormality. There was some retraction of the supraclavicular spaces during inspiration. With the patient in the sitting position, distention of the jugular veins was evident almost to the angle of the jaw bilaterally.

Two weeks later the pulse rate was 96. The temperature and blood pressure were normal. Urinalysis, blood count and Kahn and Wassermann tests were also normal. An electrocardiogram showed slight right axis deviation.

Three months later, in February, 1946, the patient's condition had become worse. She complained of a painful, pulling sensation in the mediastinum when in the recumbent position. Severe exertional dyspnea was present. About five months later and five weeks before her death examination of the chest revealed fine crepitant rales at the bases with sibilant rales over the hilar areas. Chest expansion was limited. Edge of the liver was palpable 2 cm. below the costal margin. There was edema of the ankles and feet. A month later on July 13, 1946, there were signs of early right-sided cardiac failure. The patient died two days later.

During 1944 and until August, 1945 the patient had lived about two blocks from a plant extracting and using beryllium. She then moved approximately one and one-half miles away. She first noticed symptoms on foggy days in January, 1944 when she could smell fumes from the plant. From September, 1944 to April, 1946, some three months preceding her death, five roentgenograms* of the chest were taken, one of which is shown in Figure 1.

An autopsy was performed. The significant observations made on microscopic examination of the lungs by the staff pathologist are as follows:

The alveolar walls were irregularly thickened by infiltration of lymphocytes and focal accumulation of histiocytes and foreign body giant cells. No necrosis was apparent. Occasional small purplish staining (calcified) lamellated bodies, 50–75 micra, were present in infiltrate. In patches small irregular alveoli with cuboidal epithelium enclosed by thickened walls were evident, and other patches of dilated alveoli with partly thin, partly thickened walls. Connective tissue septa were only partly involved by infiltrate; pleura showed a moderate lymphocyte infiltrate and rare histiocyte focus.

One parabronchial lymph node showed frequent, poorly demarcated foci of large mononuclear cells, frequent giant cells of Langhans' type and occasional calcified bodies. A small branch of pulmonary artery revealed marked intimal thickening due principally to connective tissue increase but with small foci and single lipophages. The anatomic diagnosis was chronic granulomatous interstitial pneumonitis and chronic granulomatous lymphadenitis. A typical area of granuloma of the lung is shown in Figure 2.

There was severe parenchymatous degeneration of the liver. Occasional nodules with giant and round cells were found. There were increased numbers of round cells in the portal

* All roentgenograms were read and interpreted by Dr. Delbert Russell, Lorain, Ohio.

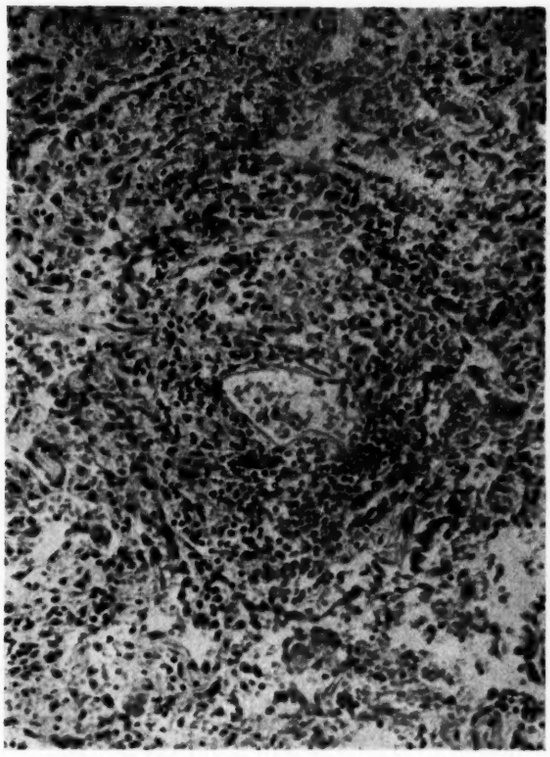


FIG. 2. Case I. Typical area of pulmonary granulomatosis. A focal accumulation of histiocytes and foreign body giant cells with infiltration of lymphocytes; no apparent necrosis.

tracts. The pathologic diagnosis was chronic granulomatous interstitial pneumonitis.

The results of beryllium determinations performed on lung tissue were as follows: mg. Be/sample—Nil or <0.000015; mg. Be/100 Gm.—Nil or <0.00008; results of similar determinations on the formalin in which the tissue was sent were as follows: mg. Be/sample —Nil and mg. Be/L.—Nil.

CASE II. A white woman, aged twenty-five at the time of her death February 17, 1948, complained of a mild non-productive cough and steady loss of weight over a period of nearly two years. The loss of weight in the two-year period was 11 pounds. About one and one-half years before she died in June, 1946 she noticed dyspnea on exertion and intermittent fever and arthralgia.

On August 12, 1946, this patient had a pulse rate of 100 with normal temperature and blood pressure. There were a few fine crepitant rales over the lung bases posteriorly but no other physical findings in the chest. Vital capacity was approximately 70 per cent of normal. Urinalysis and blood studies were normal. At this time a roentgenogram of the chest revealed

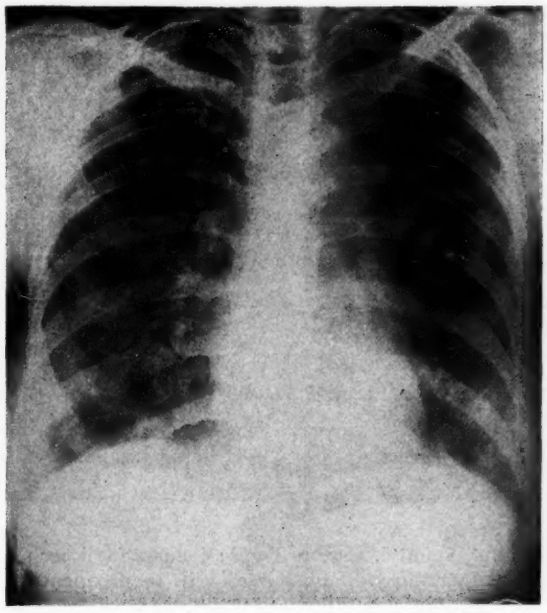


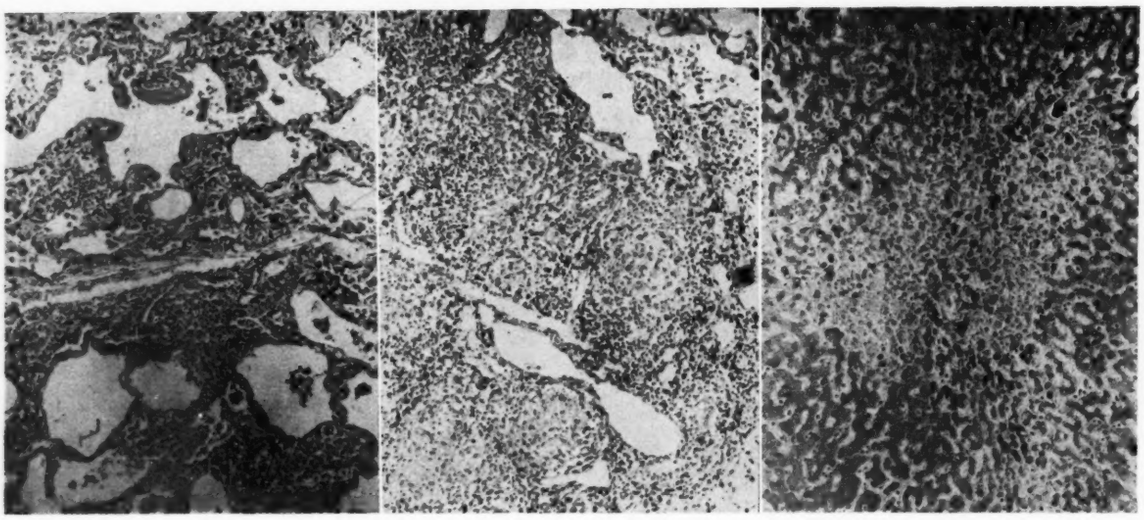
FIG. 3. Case II. Minute nodulation throughout all lung areas; five months prior to death.

accentuated hilar shadows especially on the right side with a diffuse, generalized granular appearance of all lobes of the lungs.

By June, 1947, about seven months prior to death, the patient had developed purpuric areas of the skin and mucous membranes. She had suffered from a severe pulmonary hemorrhage. Laboratory studies at this time revealed a deficiency of platelets and secondary anemia; roentgenograms of the chest showed some clearing of the lung field without associated evidence of clinical improvement. An x-ray of September 9, 1947, is shown in Figure 3.

The final roentgenograms in November, 1947 about three months prior to her death revealed a generalized granular infiltration throughout both lungs. Shortly preceding death acrocyanosis became evident, aggravated by slight exertions. Clubbing of the fingers was present. Excursions of the chest were rapid and shallow. Heart rate was 124. Fine and coarse, moist rales were audible throughout both lung fields. Occupational exposure to chemicals could not be determined. During 1941 the patient had lived approximately one-half mile from a beryllium plant. She had two normal pregnancies and deliveries in 1942 and 1944.

An autopsy was performed and the results of the microscopic examination of the tissue was made by the staff pathologist. Focal accumulations of histiocytes of foreign body and Langerhans' type with variable numbers of lympho-



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FIGS. 4, 5 and 6. Case II. Figure 4 shows focal accumulations of histiocytes of foreign body and Langhans type in lung. Lymphocytes and plasma cells are frequent in interstitial tissue of alveolar walls. Figure 5 reveals discrete tubercle formation in lymph nodes, with widening of the sinuses; no tubercle bacilli were found. Central necrosis of liver cells is seen in Figure 6.

cytes and plasma cells were found in the lungs principally in the interstitial tissue of the alveolar walls. Fibroblastic proliferation was present, usually focally arranged. However, in a subpleural zone, approximately 0.5 cm. in thickness, there was in addition to the focal lesions a fairly pronounced diffuse increase in thickness of the alvolar walls due to connective tissue proliferation and an infiltration of variable numbers of lymphocytes and plasma cells. The alveolar lumina in this latter zone were of definitely reduced size and contained a few alveolar phagocytes and occasional polymorphonuclear cells. Necrosis was not apparent in the tubercle-like lesion. Tags of loosely arranged fibrous tissue and sometimes diffuse patches of loosely arranged connective tissue were present on the pleural surfaces. A moderate amount of pink-staining granular coagulum was apparent in some alveoli. In certain areas the alveoli were greatly dilated and the atriae of bronchi presented similar dilatation. In one section there were a few small zones of hyaline fibrosis, including brownish-black pigment, with marginal histiocytes. Photomicrograph of lung tissue is seen in Figure 4.

There were many focal accumulations of histiocytes and an occasional giant cell in the lymph nodes. (Fig. 5.) A moderate amount of hyaline fibrosis was present in patches. The tubercles were discrete and showed no tendency to conglomeration; the sinuses were widened. Sinuses were prominent in the spleen but contained only a few red cells. There was an increase of connective tissue of the pulp. In an occasional nodule there was a discrete accumulation of histiocytes with reticulo-endothelial cells and rarely with a giant cell of foreign body type. None of these were apparent in the pulp. An occasional small patch of hyaline fibrosis was detected in the lymph nodules.

Principally in the central areas of the liver, Figure 6, but also to a slight extent in the midzonal areas, there were small patches of necrotic liver cells, with a moderate number of polymorphonuclear cells at times in the vicinity of the oxyphilic liver cells.

Pathologic diagnosis was interstitial granulomatous pneumonitis, granulomatous lymphadenitis, chronic passive congestion of the spleen, slight toxic splenitis and moderate focal necrosis of the liver.

CASE III. A twenty-five year old white woman first noticed a dry cough in December, 1944. Dyspnea on exertion did not develop until a year later following the birth of a second child. At this time the patient also had anorexia, some loss of weight and pain in the substernal region which was accentuated by attempted deep inspiration. All of these symptoms became progressively worse.

At the time of examination on February 10, 1948, a small amount of exertion produced dyspnea, acrocyanosis and a disagreeable spasmodic cough productive of mucoid sputum devoid of blood. The "coughing spells" were

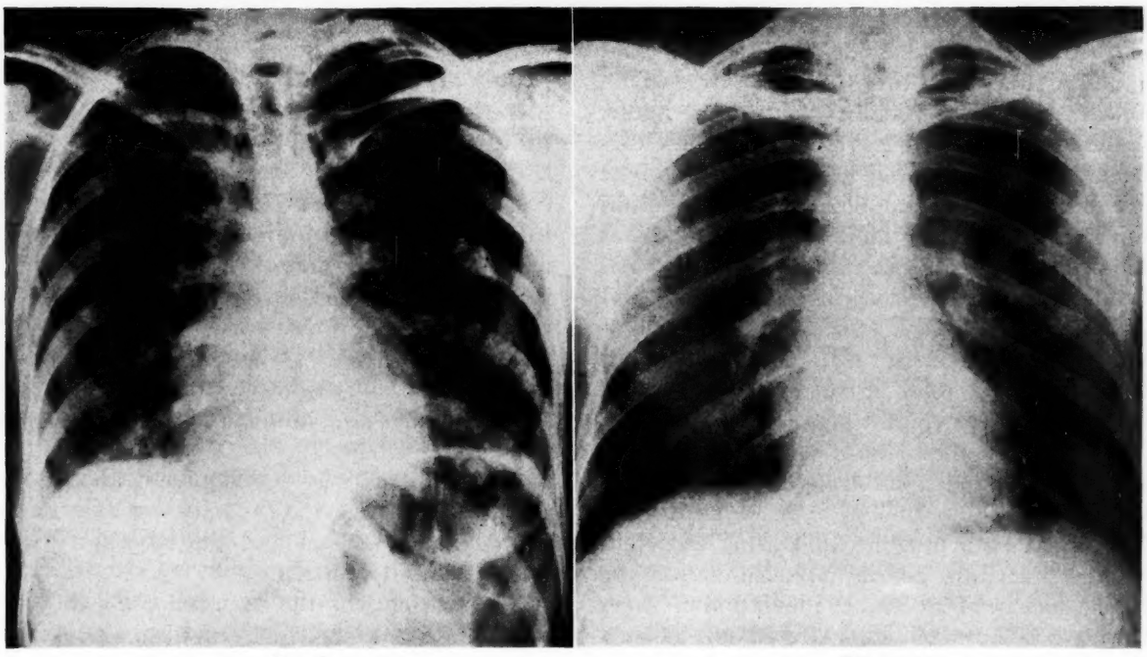

FIG. 7 FIG. 8

FIG. 7. Case III. Bilateral pneumothorax complicating diffuse pulmonary granulomatosis.
FIG. 8. Case VII. Punctate type of granular-appearing infiltration diffusely scattered through both lung fields.

worse in the morning and were aggravated by breathing cold air. The patient was afebrile throughout the illness.

The patient weighed only 85 pounds. Pulse rate was 86 and the blood pressure was 90/65. Vital capacity was one-third of calculated normal and the lungs were resonant to percussion. Expansion of the chest was greatly limited. Fine, moist rales and sibilant rhonchi were audible in both lung fields. There was severe acrocyanosis with clubbing of the fingers. Routine urine and blood studies did not reveal any serious abnormalities either at this time or a month later. Roentgenograms of the chest disclosed a generalized, diffuse, granular, streaky infiltration throughout both lung fields. There was bilateral pneumothorax. (Fig. 7.)

The only possible occupational exposure occurred while the patient worked in a toothpaste packing room and inhaled a considerable amount of paper dust during the latter months of 1943. Her husband worked in a beryllium plant for about eight weeks after their marriage in December, 1942, but the patient did not handle any of his working clothes nor did any respiratory symptoms develop during this period. Exertional dyspnea became apparent in 1945 immediately after the birth of a second child.

A roentgenogram of this patient's chest on March 23, 1948, is shown in Figure 7 with bilateral pneumothorax complicating diffuse pulmonary granulomatosis.

CASE IV. A white woman, who was thirty-four years old when first observed in April, 1945, complained of chills, tightness and pressure over the chest, some shortness of breath and palpitation of the heart on slight exertion. She had lost 10 pounds during the preceding eight months. The symptoms had become progressively more severe and included a change in the color of her fingernails. The symptoms were reported to have begun in April, 1942, eight months after a pregnancy which was the patient's fourth.

Physical examination revealed engorgement of the veins of the eyegrounds and cyanosis of the lips. The chest was resonant throughout, but expansion was definitely diminished. Fine, moist rales were heard throughout the lungs, especially over the bases; the edge of the liver was barely palpable. Acrocyanosis and slight deformities of the finger tips were present although urinalysis and routine blood studies revealed no particular abnormalities. A roentgenogram showed a diffuse miliary type of infiltration throughout both lung fields giving a groundglass appearance. The hilar and main bronchial trunks showed increased markings in both lung fields.

During her three week hospitalization she received calcium gluconate intravenously and aminophylline. For two weeks she was given 20,000 units of penicillin every four hours. Slight improvement occurred with some clearing of the apices of the lung, lessened fatigue and shortness of breath on exertion and diminution in the amount of sputum. The patient was somewhat improved six months later but still complained of dyspnea on exertion. Chest examination revealed some limitation of expansion and sibilant rhonchi were heard throughout the hilar areas and bases; vital capacity was 82 per cent of calculated normal. Laboratory studies were essentially within normal limits and roentgenograms of the chest disclosed a diffuse miliary type of infiltration throughout both lung fields. During the eight months preceding her initial examination the patient had been exposed to inhalation of fumes from a beryllium plant located about 100 feet from her residence. She was not, however, employed by the plant or apparently otherwise exposed.

On June 29, 1948, she gave birth to a normal boy following an uneventful pregnancy. When re-examined on October 1, 1948, she stated that she had improved considerably since leaving the neighborhood of the beryllium plant. The vital capacity was increased to 90 per cent of the computed normal and the acrocyanosis and clubbing of the fingers were comparatively less pronounced.

CASE V. A twenty-one year old white woman was first examined in September, 1947, her symptoms dating from about nine months previously when she had developed a spasmodic cough with some production of mucus. Shortly thereafter she noticed some dyspnea on exertion which was aggravated on damp days. Coughing spells were also more acute on damp days and in the mornings. Substernal pain and tightness became apparent, and a month or two before her visit her fingernails turned blue and showed a tendency to curve downward. Chills and fever were also reported.

On the day of admission to the hospital in September, 1947 the patient developed dyspnea with chills and fever. Her temperature was 104°F., pulse 134 and respiration 35. Acrocyanosis with clubbing of the fingers were evident. A persistent cough existed, perspiration was profuse and the patient's breathing was rapid and shallow. Fine and coarse moist rales were heard over the right lung and sibilant rhonchi over both lungs. Chest expansion was greatly limited. Urinalysis was negative and the blood count was within normal limits except for a leukocytosis of 10,450.

Roentgenograms, Figure 8, revealed a widespread, diffuse, miliary-like, granular-appearing infiltration throughout both lungs. Each granule appeared to be discrete. The patient was given oxygen almost constantly for a week and penicillin for two weeks. Streptomycin was administered for five days. A roentgenogram taken at the time of discharge from the hospital seventeen days after admission did not show any appreciable change.

The patient was re-examined about two months later. Her vital capacity was 86 per cent of calculated normal and the laboratory tests were essentially normal.

This patient for the approximate five years from 1940 to 1945 had lived within one block of a beryllium plant. In November, 1945 she moved about 1 mile away but returned to the earlier address in January, 1947 shortly before the first symptoms became manifest. The same month she gave birth to a son. She was examined on June 29, 1948, and stated that since moving to her new residence three months ago she had noticed a definite improvement. The vital capacity was 90 per cent of normal but physical examination of the chest was the same as on the last examination.

CASE VI. A white woman, twenty-eight years old, first noticed symptoms in December, 1946. These symptoms of weakness and loss of ambition became progressively worse. Approximately five months later in May, 1947 she developed a spasmodic non-productive cough, more pronounced in the mornings on awakening. About one month later the cough became productive with mucus occasionally slightly tinged with blood. The cough grew worse when she inhaled fumes from a beryllium plant near which she lived. Fever and chills at frequent intervals developed in July, 1947. At this time she had a fever of over 101°F. The symptoms of dyspnea were more evident on humid days while the patient had lost 22 pounds between the onset of her symptoms and the time when she was first observed on November 24, 1947. A bluish color of her fingernails was noted during the summer of 1947 as well as downward curving of the fingernails. On May 28, 1945, the patient completed her second pregnancy.

On examination acrocyanosis was noted with slight clubbing of the finger tips. Systolic pressure was 100, pulse rate was 120, the vital capacity was 68 per cent of normal and the chest expansion was definitely diminished. Fine crackling rales and sibilant rhonchi were audible, especially in the hilar and basal areas of the lungs. Resonance of the lungs was normal.

Roentgenograms of the chest revealed a diffuse granular type of infiltration throughout both lung fields. The granular areas were somewhat discrete and generalized haziness was shown throughout both lungs. Examination of the urine and blood did not reveal any serious abnormalities except a white blood cell count of 13,300.

This patient had lived approximately one block from a beryllium plant for the four years preceding her first examination in November, 1947, i.e., over three years before any symptoms became manifest. She was last seen in June 1, 1948, and had improved definitely since leaving the neighborhood of the beryllium plant. However, she still complained of cough and shortness of breath on exertion. Examination of the chest did not reveal anything new. The vital capacity was 68 per cent of computed normal.

Case VII. A white man aged twenty-seven developed a cough with chills and fever in December, 1944 while he was in the army. Roentgenogram of the chest at that time was negative. The chills, fever and cough persisted with the symptoms most pronounced early in the morning. The cough was non-productive. The patient had lost 8 pounds during the six months prior to December 1, 1947, at which time he complained of weakness and exertional dyspnea with some substernal pain and tightness of the chest on inspiration. The symptoms were more evident on humid days.

On examination there was definite acrocyanosis with slight clubbing of the fingers and toes. Pulse rate was 78. Chest expansion was restricted and the vital capacity was 74 per cent. Sibilant rhonchi were heard intermittently over both lung bases. Roentgenograms of the chest (Fig. 8) showed slight enlargement of the hilar shadows but there was no suggestion of nodulation. A punctate type of granular-appearing infiltration was diffusely scattered through both lung fields. The patient has been under observation since that time and has grown progressively worse. Laboratory tests are essentially normal.

The patient had worked in and around a beryllium plant for six weeks during the summer of 1941. His work consisted principally in the construction and handling of bags of beryllium oxide and what he thought was beryllium sulfate. He cleaned out several sulfate vats. He did not complain of any illness during this period, but dust from the bags irritated his throat and produced a cough. With the exception of these six weeks, he was either working on a railroad or serving in the armed forces until February, 1946. Since that time, he has been employed in a radiator plant where his work consists of the chemical testing of iron for sulfur, silica and carbon. He has worked with calcium carbide frequently.

He was last examined on June 29, 1948, at which time he complained of frequent attacks of hyperpyrexia associated with dyspnea. These attacks had occurred at intervals of from two to three times a week during the previous two months. Examination at that time revealed the same chest findings as on the last visit. The vital capacity was 47 per cent of normal. The weight was 124 pounds and the temperature 98°F.

Case VIII. A white woman thirty-nine years old began to exhibit symptoms in August, 1946. At that time she developed a cold with a cough which persisted until December 1, 1947, the time of her first examination by us. At first the cough was non-productive but after several months sputum was present in the morning. During inspiration and the coughing attacks she was aware of substernal pain and tightness of the chest. In July, 1947 she experienced dyspnea on exertion which has grown progressively worse. By December, 1947 she was able to do only light housework without discomfort. During the entire illness her appetite was good and she gained 8 pounds from June, 1947 to December, 1947.

Physical examination did not disclose any acrocyanosis or abnormal changes of the fingers. Pulse rate was 76. Expansion of both lungs was adequate and equal. Vital capacity was 95 per cent of computed normal although a few wheezy rales were audible throughout the hilar areas. Routine laboratory tests were essentially normal. Roentgenograms on December 1, 1947, Figure 9, revealed a slight enlargement of the hilar shadows but no nodulation. There was a punctate type of granular-appearing infiltration diffusely scattered through both lung fields.

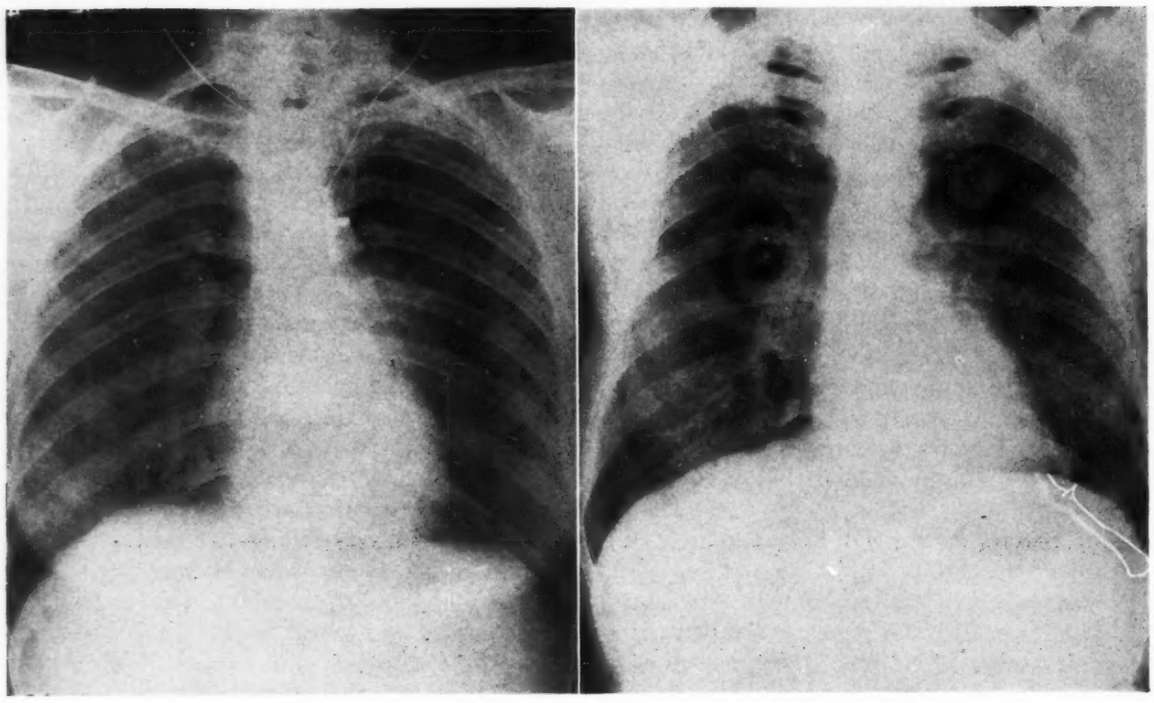

FIG. 9 FIG. 10

FIG. 9. Case VIII. Diffuse granular infiltration of lungs.
FIG. 10. Case X. Roentgenogram of chest shows diffuse granular infiltration.

This patient was employed in the laboratory of a beryllium plant from November, 1943 to March, 1944. During this period she did not have any respiratory complaints, but because of a papular rash of the hands and forearm was advised to give up her work. For the next three years she resided in northern California and Oregon.

The patient was examined on June 8, 1948, and stated that except for some exertional dyspnea she felt decidedly improved since the last examination. She has not experienced any cough during the last month. Examination of the chest failed to reveal any additional findings since the previous examination. The vital capacity was 77 per cent of normal.

CASE IX. A white man aged twenty-six complained of exertional dyspnea and a persistent cough which had been present from January, 1946 to May 20, 1947. In January, 1946 he had the "flu" with accompanying cough, shortness of breath and arthralgia. The cough was persistent and produced mucoid sputum without blood. He did not have fever. His appetite was poor and he lost 50 pounds in the first twelve months of his illness.

On physical examination his temperature was found to be normal and his pulse rate 98. Chest expansion was diminished and vital capacity was approximately 50 per cent of normal. The lungs were resonant to percussion but a few fine crepitant rales were heard over both apices and bases. Roentgenogram revealed an extensive generalized granular appearance of all lung lobes. Laboratory studies were essentially normal.

This patient had worked in the fluoride process department of a beryllium plant during the last eight weeks of 1941. His reason for leaving this work was development of cough and shortness of breath. However, he has not experienced chemical or occupational exposure since that time.

His course since October, 1947 does not indicate any clinical improvement although he continued to work contrary to medical advice.

CASE X. A white man, forty-eight years old at the time of examination on April 26, 1948, complained of a persistent spasmodic productive cough, anorexia with weight loss and progressive exertional dyspnea beginning in early October, 1947. Since the onset of the illness, he lost over 40 pounds. The coughing attacks have become more frequent and longer in duration and productive of a greenish sputum. Exertional dyspnea became so pronounced that he was forced to give up his work. At present exertional dyspnea is often accom-

panied by vertigo. He has experienced some mild chills and at times stated that he "felt hot."

Physical examination revealed a normal temperature, pulse rate of 75 and respiratory rate of 20. There was no respiratory distress or acrocyanosis and changes of the finger tips. The blood pressure was 96 mm. Hg systolic and 70 mm. Hg diastolic. The vital capacity was 82 per cent of normal and the breath holding test was 20 seconds.

The chest expansion was slightly diminished with the patient's complaint of substernal discomfort at the limit of inspiration. The percussion note was resonant and equal throughout. Breath sounds were of normal character throughout both lungs and no adventitious sounds were audible. Pulmonary roentgenograms showed a diffuse, granular and fibrous-appearing infiltration throughout the parenchyma of both lungs. There was some associated prominence of the hilar shadows but no nodulation at the hila. (Fig. 10.) Laboratory studies of the blood and urine were essentially normal.

The patient was employed in a beryllium plant on April 30, 1945, and first worked for seven days handling beryllium fluoride until transferred to the crystallizing sulfating department for a period of nine days previous to onset of symptoms on May 30, 1945, when he developed exertional dyspnea and a productive spasmodic cough. The clinical and roentgenologic diagnosis at that time was acute chemical bronchitis probably due to beryllium salts. He recovered from this initial attack and returned to work in the same plant on July 9, 1945, in the ore grinding mill. After an additional ten days of work he developed a second attack of acute bronchitis and following complete recovery he was given a medical release from the industry on September 11, 1948, because of his recent illness.

This patient was seen on June 28, 1948, and still complained of a spasmodic cough, shortness of breath and loss of weight. Examination of the chest failed to reveal any changes. The vital capacity was 71 per cent of normal. His weight was 145 pounds.

SUMMARY*

From a review of the pertinent data in ten cases, including two patients who died, it is apparent that a characteristic sequence of clinical symptoms and the typical appearance of roentgenograms permit accurate diagnosis in chronic pulmonary granulomatosis. A history of exposure to certain chemical hazards may aid in the diagnosis, but conclusive evidence of exposure cannot always be secured. Specific treatment is not available. Certain drugs may be used symptomatically with some degree of relief of subjective symptoms. The most effective treatment at present is adequate rest and the avoidance of respiratory infection. All evidence points to early diagnosis as the prime requisite for proper treatment.

* Since this report was submitted three additional patients have been seen. One patient died and necropsy was performed with findings similar to those previously reported.

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Review

Prognosis of Acute Myocardial Infarction*

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Clinical expressions of coronary artery disease vary greatly, ranging from immediate death following sudden complete occlusion of a coronary artery to a variety of phenomena resulting from the encroachment upon cardiac reserve and cardiac function of a more gradually reduced blood supply to the myocardium.

This paper records an analysis of 240 cases of acute coronary artery occlusion or acute coronary insufficiency of such degree as to produce myocardial infarction. The purpose of the study is to determine, by a detailed analysis of the hospital records of patients with acute coronary artery occlusion or acute coronary artery insufficiency resulting in infarction, whether any of the data in the clinical history, physical examination or laboratory investigations are consistently useful in predicting the train of events following the acute episode.

In the first part of the report particular note has been made of factors having a bearing on immediate mortality. The term immediate mortality has been arbitrarily used to connote death within thirty days of the acute attack. In the second part advantage has been taken of an unusual opportunity to correlate data acquired from study of the acute heart attack with information concerning patients who were alive after the thirty-day period. One hundred forty-three of the two hundred forty patients whose records were analyzed survived the acute attack. Follow-up data were obtained concerning all of them and information was available regarding the amount of physical activity in which 120 of these survivors were able to participate.

We recognize the limitations imposed upon this study by the nature of the material. Many patients who develop acute coronary occlusion and myocardial infarcts die immediately before reaching a hospital, others are too sick to be moved, while still others are not considered sick enough to be taken to a hospital.[1]

The diagnosis of coronary occlusion with myocardial infarction was listed in 591 clinical records from the wards of the Vanderbilt University Hospital during the years 1925 to 1946 inclusive. Two hundred forty cases satisfying one or more of the following criteria constitute the material for this study: (1) The typical clinical picture of pain not necessarily produced by increased demands on the cardiovascular system nor relieved by nitrites or rest, and usually accompanied by signs of shock, tachycardia, fall in blood pressure, elevation of temperature, leukocytosis and acceleration of the erythrocyte sedimentation rate. (2) Electrocardiographic changes indicative of acute local myocardial damage. (3) The demonstration at autopsy of a recent myocardial infarction with or without a completely occluded coronary artery, or complete occlusion of a coronary artery with or without an acute infarct. Thus there was convincing evidence in each case that a recent acute episode related to coronary

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artery disease had ocurred and that serious damage either to the myocardium or to a coronary artery or both was present.

Three hundred fifty-one of the five hundred ninety-one cases were not included because: (1) The criteria necessary for a positive diagnosis were not fulfilled; (2) the hospital admissions were for diagnosis or evaluation of physical status or for rehabilitation some time after an episode of acute coronary disease; (3) a few patients with acute coronary disease died so soon after admission to the hospital that there was no opportunity to obtain data necessary for this study.

The record of only one attack was analyzed in each case. One hundred eighty-four records were of first attacks of myocardial infarction, the remaining fifty-six records were of patients observed during a second or subsequent seizure.

In reviewing the records it was frequently difficult to determine exactly when the acute attack began. Often there was a description of repeated, severe episodes of substernal pain followed within a few hours or days by a more severe but otherwise similar episode accompanied by the symptoms, signs and laboratory findings of myocardial infarction. We believe that these premonitory symptoms were those of coronary artery failure[2] without permanent damage to cardiac muscle, and that when the blood supply to the myocardium became so deficient as to result in death of muscle the typical picture of myocardial infarction developed.

In the statistical interpretation of the data in this report differences of 2.6 standard deviations or more (a probability of .01 or less) have been considered to be "significant." Differences of more than twice the standard deviation are considered "probably significant." In Tables IV, VI, X and XI the asterisks denote that there is a significantly greater mortality among those cases in which the phenomena so marked are present than among those in which they are absent. Obviously conclusions cannot be drawn from percentages computed on small numbers.

IMMEDIATE PROGNOSIS OF MYOCARDIAL INFARCTION

Sex and Age Incidence. In the group of 240 patients with acute manifestations of coronary artery disease there were 175 males and 65 females, a ratio of 2.7 to 1. There were ninety-seven deaths within thirty days of the acute episode, or an immediate mortality of 40.4 per cent. Among the 184 patients whose first acute attack was studied the ratio of males to females was 2.3 to 1. Figure 1 demonstrates the frequency distribution by age and sex among these patients. In this group the immediate mortality was 36.4 per cent. As was to be expected the immediate mortality was higher, 53.6 per cent, with the occurrence of a second or third attack. The mortality in the acute stage in other reports in the literature varies from 25 to 45 per cent.[3–11]

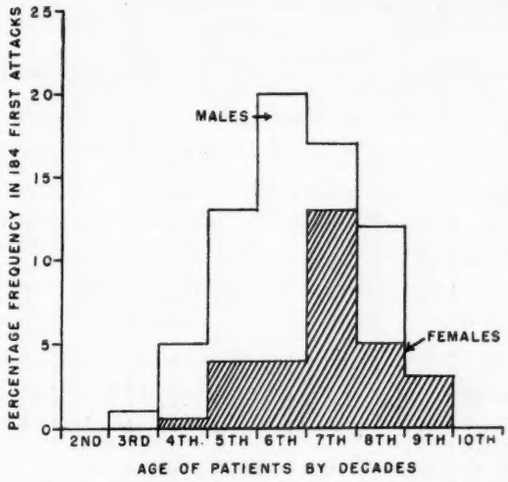

FIG. 1. Frequency distribution by age and sex.

Table I is an analysis of the group of 184 patients whose first acute attacks of coronary artery disease were studied with special reference to sex, age and immediate mortality. The mean age at the time of the attack was sixty years, for the males fifty-eight years and for the females sixty-four years. The immediate mortality rate was slightly higher in females than in males.

The relatively larger number of females over fifty years of age was probably a contributing factor. In those persons fifty years or older there were more deaths within thirty days of the acute cardiac episode than among those under fifty. There were

TABLE I
FIRST ATTACK: AGE AND SEX INCIDENCE, IMMEDIATE MORTALITY
(DEATHS IN THIRTY DAYS)

Age in Years	Total		Male		Female	
	No. of Patients	Immediate Mortality (per cent)	No. of Patients	Immediate Mortality (per cent)	No. of Patients	Immediate Mortality (per cent)
20–29	2	100	2	100		
30–39	10	20	9	11	1	100
40–49	31	19	23	17	8	25
50–59	44	34	37	38	7	14
60–69	55	38	31	32	24	46
70–79	32	47	22	41	10	60
80+	10	60	5	60	5	60
Total	184	36	129	33	55	44

eleven males with acute coronary artery occlusion under forty years of age and only one female. These data are remarkably similar to those reported by other investigators.[3–11]

Although the percentage of total admissions to Vanderbilt University Hospital of patients with manifestations of acute myocardial infarction increased significantly during the period 1925 through 1946, the per cent of immediate mortality from this disease during the periods 1925 through 1934, and 1935 through 1944, and for the years 1945 and 1946 did not vary significantly.

Racial and Seasonal Incidence. No conclusion regarding racial incidence can be drawn from data presented here because the distribution of patients by race, 229 white and 11 negro patients, was highly selective.

Burch[12] states that he has rarely encountered angina pectoris in negro males and not at all in negro females. In this study five of seven negro males and two of four negro females gave histories of typical angina pectoris preceding myocardial infarction. The sudden development of congestive heart failure or an exacerbation if failure is already present has been cited[13] as the chief manifestation of myocardial infarction in the negro race. Four of eleven negroes in this group had no congestive failure at any time and three of them had no pain with their attacks. All but two had hypertension. Three of the eleven died within thirty days of their acute attack. No significant difference between negro and white patients with regard to the clinical picture, course, complications, prognosis or immediate mortality was observed.

TABLE II
SEASONAL INCIDENCE AND IMMEDIATE MORTALITY
(DEATHS WITHIN THIRTY DAYS)

Season	Month of Attack	No. of Cases	Per Cent of all Cases	No. of Deaths in Thirty Days	Per Cent Immediate Mortality
Winter	December, January, February	72	30	32	44
Spring	March, April, May	52	22	16	31
Summer	June, July, August	49	20	21	43
Fall	September, October, November	67	28	28	42
Total		240	100	97	40

More persons had attacks in the three coldest months of the year than in the three warmest months. (Table II.) Bean[3] and Munck[14] also found a higher incidence during the winter months.

Physical Activity at Onset of Attack. Table III demonstrates that in the majority of cases (64 per cent) the acute episodes of coronary occlusion occurred during complete inactivity. They occurred during mild activity in 14 per cent and during moderate or vigorous activity in 22 per cent of the cases. These findings agree with those of Master and his associates.[15]

Symptoms. Not every patient whose myocardium is damaged by sudden interruption of the flow of blood through a coronary

artery experiences symptoms. Death may occur suddenly and under these circumstances the presence or absence of symptoms may not be known. Moreover, Blumgart and Schlesinger[16] have shown that gradual occlusion of a coronary artery with production of myocardial fibrosis may occur asymptomatically. Nevertheless, sudden interference with the blood supply to the myocardium is commonly associated with a variety of symptoms. A list of these, with the exception of pain, as noted in the 240 hospital records appears in Table IV. The incidence of these symptoms and the associated immediate mortality for each are indicated. The symptom of pain is of such importance that it will be discussed at length.

TABLE III

PHYSICAL ACTIVITY AT ONSET OF ATTACK

Activity	No. of Cases	Per Cent Incidence
Sleeping	38	24
Rest in bed	44	28
Inactivity (4 hr.)	19	12
Mild activity	22	14
Moderate activity	28	18
Vigorous activity-sustained	4	3
Vigorous activity-short time	1	1
Total	156*	100

* Amount of activity not known in other cases.

In considering the prognostic significance of any of these symptoms it is well to remember that the over-all immediate mortality for the entire series of patients studied was 40.4 per cent. It is noteworthy that the existence of any one of three of the symptoms commonly experienced made the prognosis significantly worse. These were dyspnea, cloudy sensorium and clammy sweating. All three are frequently associated with grave dysfunction of the heart, the first with retrograde pulmonary congestion and the latter two with diminished cardiac output. Hiccough was described in only six patients, all males. All terminated fatally.

Pain. Table V shows the distribution of cases and per cent mortality according to location, radiation, type, severity and presence or absence of pain. A number of individuals experienced pain in more than one location with radiation in more than one direction. This is reflected in the table. Usually pain was located in the precordial or substernal regions. Abdominal pain alone was experienced by sixteen patients, ten of whom died within a thirty-day period following the acute attack. There was no statistically significant relationship to the immediate mortality of either location or radiation of pain.

Pain was most frequently described as constricting or crushing in character. No proper evaluation of the severity of a heart attack could be made on the basis of the patient's statement regarding the intensity or character of the pain. An individual with mild pain was just as apt to expire during the acute attack as the patient with severe pain.

Boyd and Werblow[17] observed that pain subsides when congestive cardiac failure develops following acute coronary artery thrombosis and that pain is less likely to be experienced if congestive failure is already present at the time of onset of the symptoms of acute coronary artery occlusion. In the eighty-one patients in this series in whom congestive failure was present at the onset of symptoms of the attack the incidence and severity of pain was as follows: no pain, eleven; mild pain, nine; moderately severe pain, twenty-two; severe pain, twenty-seven; severity unknown, twelve. These figures relating to the occurrence of pain with myocardial infarction in the presence of congestive heart failure differed but little from those for the occurrence of pain in the absence of congestive failure.

Painless Attacks. Considerable controversy has developed in the literature concerning the frequency of painless myocardial infarction. In his review of the subject Kugel[18] found that the incidence varied in the different reports from 0.86 to 75 per cent. One important reason for this dis-

agreement may be the lack of uniform use of the word pain by the patient and the historian. To clarify this point 229 of our cases with adequate records regarding pain were grouped as follows (Table v): (1) Pain was a definite complaint. There were 205 patients in this group. Seventy-four (36 per cent) died within thirty days. (2) The word pain was not used in the history; nevertheless, a sense of either thoracic oppression, constriction or discomfort was recorded. There were four patients in this group; all survived the thirty-day period following the attack. (3) No pain or discomfort was present. These were genuine examples of "silent" coronary occlusion. There were twenty patients (somewhat less than 10 per cent of the total number) in this group; thirteen (65 per cent) of these patients died within thirty days. A presenting symptom in thirteen of the twenty individuals who experienced no pain or discomfort was dyspnea.

It has been noted previously that the mortality following silent coronary artery occlusion is high.[4] In our series the percentage mortality for patients with no pain or discomfort was 65 per cent whereas for those who experienced pain it was 36 per cent.

Past History. In a study of coronary artery occlusion the past history would seem to be of particular importance insofar as it is related to the status of the patients' cardiovascular system or to any diseases or

TABLE IV

SYMPTOMATOLOGY OF THE ATTACK: INCIDENCE AND PROGNOSTIC IMPORT

Symptom	Cases with Symptom Present		Cases with Symptom Absent	
	Incidence (per cent)	Immediate Mortality (per cent)	Incidence (per cent)	Immediate Mortality (per cent)
Dyspnea*	71	47	29	20
Restlessness	40	45	60	35
Weakness	38	44	62	36
Nausea	35	38	65	40
Vomiting	33	39	67	40
Sweating, clammy*	28	67	72	29
Cough	28	45	72	32
Cloudy sensorium*	28	65	72	29
Sweating, profuse	26	30	74	43
Vertigo	8	32	92	40
Palpitation	7	32	93	40
Fatigue	7	38	93	40
Stokes-Adams syndrome	5	33	95	40
Hiccough*	2	100	98	37

* Significant.

TABLE V

DISTRIBUTION OF CASES AND PER CENT IMMEDIATE MORTALITY ACCORDING TO LOCATION, RADIATION, TYPE, SEVERITY AND PRESENCE OR ABSENCE OF PAIN

Location, Radiation, Type and Severity of Pain	Incidence (per cent)	Mortality (per cent)
Location: substernal or precordial	79	33
epigastric	20	37
abdominal	6	43
interscapular	4	33
arms only	1	67
other	2	20
Radiation: left arm	26	31
both arms	23	32
shoulders	22	24
neck and jaws	8	18
back	6	58
abdomen	4	29
right arm	2	33
other	3	
non-radiating	32	47
Type: constricting or crushing	60	23
sharp or knife like	30	46
dull	23	33
aching	18	29
choking	8	15
burning	7	27
boring	2	
other	4	33
Severity: severe	45	38
moderately severe	34	27
mild	11	38
Total with pain	90	36
Pain denied, chest discomfort present	2	
No pain, no discomfort, "silent"	8	65
Total without pain	10	54

abnormalities which render the patient more susceptible to arterial occlusion and more likely to die as a result of damage to the myocardium should sudden occlusion of a coronary artery occur.

It is noteworthy that the analysis of our records of 240 patients with myocardial infarction revealed that sixty-six patients (28 per cent) gave no history of symptoms specifically referable to the cardiovascular system prior to the acute attack. The immediate mortality among these patients was essentially the same as for the group as a whole. (Table VI.)

TABLE VI
HISTORY RELATIVE TO STATUS OF PATIENTS' CARDIOVASCULAR SYSTEM AND ASSOCIATED DISEASES

History	Cases in which Present		Cases in which Absent	
	Incidence (per cent)	Immediate Mortality (per cent)	Incidence (per cent)	Immediate Mortality (per cent)
Previous heart complaints (excluding dyspnea)	72	42	28	38
Hypertension	54	37	46	41
Angina pectoris	54	40	46	41
Congestive failure*	40	55	60	30
Gallbladder disease (clinical and autopsy findings)	13	52	87	38
Diabetes mellitus†	13	57	87	38

* Significant.
† Probably significant.

1. *Congestive Heart Failure:* A past history of congestive heart failure was obtained in over one-third of the patients in this series (Table VI) and the vast majority of patients with such a history presented signs of congestive heart failure at the onset of the acute episode of coronary artery occlusion. The immediate mortality in this group of patients was 55 per cent in contrast to 30 per cent for the group in which there was no history of cardiac failure preceding the acute attack of coronary occlusion. This corresponds closely with the observations of others.[5,11,19,20]

2. *Angina Pectoris:* There was a past history of angina pectoris in approximately one-half of the patients in this series. (Table VI.) However, the immediate mortality for patients with previous angina pectoris was essentially the same as for those who had not had this symptom. Fisher and Zuckerman[19] reported a less favorable prognosis for patients giving a history of angina pectoris whereas Levine and Rosenbaum[4] believed that angina pectoris in the past improved the outlook of the individual with an acute myocardial infarction. Discussing coronary artery disease in patients under forty years of age, Glendy and associates[21] reported that a past history of angina pectoris improved the prognosis of occlusion. In our series eight patients under forty years of age had had angina pectoris. Four died within thirty days of the acute episode. The over-all immediate mortality in this age group was 36 per cent.

3. *Hypertension:* All patients with a history of systolic blood pressure greater than 150 mm. Hg or diastolic pressure greater than 100 mm. Hg were considered to have hypertension. According to this classification a little over one-half (54 per cent) of the patients in the series had hypertension. (Table VI.) The incidence of hypertension was significantly higher among the females (69 per cent) than among the males (48 per cent). The immediate mortality following coronary occlusion among all hypertensive patients was essentially the same as among those whose blood pressure had been normal. The incidence of hypertension in studies of acute coronary occlusion or myocardial infarction, as reported in the literature, varies from 41 to 70 per cent.[4,9,22–25] The opinion that the previous existence of hypertension has no prognostic significance in this condition has been expressed.[11,19,26] Levine and Rosenbaum,[4] in their study of 208 cases of myocardial infarction, found the immediate mortality higher among patients with hypertension.

4. *Hypertension and Angina Pectoris:* Seventy-two patients with a history of hypertension also experienced attacks of angina pectoris prior to the acute episode of coronary artery occlusion. It is apparent (Table VII) that neither the presence nor absence of a history of angina pectoris and hypertension, alone or combined, affected the immediate mortality in our group of patients. Levine and Rosenbaum[4] found that a history of angina pectoris without hypertension was associated with a more favorable outlook than a history of hypertension in the absence of previous angina pectoris.

TABLE VII
RELATION BETWEEN IMMEDIATE MORTALITY AND A HISTORY OF HYPERTENSION AND ANGINA PECTORIS

	Incidence (per cent)	Immediate Mortality (per cent)
Neither previous angina pectoris nor hypertension	22	45
Previous angina pectoris without hypertension	22	41
Hypertension without previous angina pectoris	24	35
Both previous angina pectoris and hypertension	33	38

Of the women in our series 14 per cent had had neither previous angina pectoris nor hypertension. Eppinger and Levine[27] observed that myocardial infarction occurred very rarely in women in the absence of a history of either angina pectoris or hypertension (two of a total of fifty-nine women).

5. *Associated Diseases:* (1) *Diabetes mellitus*—Thirty (13 per cent) of the patients in our series had diabetes mellitus. (Table VI.) The incidence was higher in females, thirteen of sixty-three (21 per cent), than in males, 17 of 174 (10 per cent). Similar observations have been recorded by others.[3,5,9,10] About one-half (17) of the patients with diabetes mellitus died within thirty days of the acute heart attack. The presence or absence of previous hypertension was known in all the females with diabetes mellitus and in sixteen of the seventeen males. It is of interest that while only nine of the sixteen males in this group had hypertension, twelve of the thirteen female diabetics had elevated blood pressure.

(2) *Disease of the Gallbladder*—Breyfogle[28] and Walsh and his associates[29] found a higher incidence of disease of the gallbladder in patients with coronary artery disease than in those with normal or only minimally sclerosed coronary arteries. Pertinent information was available in 228 of the clinical records analyzed by us. (Table VI.) Twenty-nine records (13 per cent) contained either clinical or postmortem evidence of gallbladder disease. To determine the incidence of gallbladder disease in a general group of patients examined at autopsy 231 protocols were reviewed. These were selected so as to correspond with relation to age, race and sex to the records which are the subject of this study. Protocols describing advanced coronary artery disease were excluded. Gallbladder disease was considered to have existed if either stones or cholecystitis were recorded, or if cholecystectomy had been performed during life. The incidence of gallbladder disease in this control group was 22 per cent. The incidence of gallbladder disease in our two series does not confirm the findings of other authors.[28,29]

(3) *Other Diseases*—Utilizing the aforementioned method of comparison we could establish no correlation between the occurrence of peptic ulcer and coronary artery disease. However, it is of interest and probably significant that eleven (17 per cent) of the sixty-five patients with coronary disease examined at autopsy had gastrointestinal diverticula while they were found in only twelve (5 per cent) of the 231 control patients.

Family History. The family history relating to heart disease was recorded in 192 cases. In 45 per cent of these a family history of heart disease was present. Other studies[3,25]

reveal a similar incidence of heart disease in the families of cardiac patients. The presence or absence of a family history of heart disease bore no significant relationship to the immediate mortality in our series.

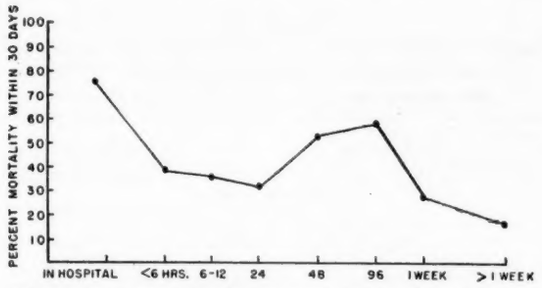

FIG. 2. Mortality in relation to time elapsing between attack and hospitalization.

Habits, Occupation and Habitat. We found it impossible to determine satisfactorily any effect of tobacco, alcohol, coffee or inadequate or irregular meals on prognosis. In general no very convincing relationship between occupation and immediate mortality could be recognized. However, there was higher immediate mortality (54 per cent) among patients living in rural areas than among those living in cities (35 per cent) and among farmers (58 per cent) than among professional men and tradesmen (30 per cent). These differences are statistically significant. They are best explained perhaps by the fact that the percentage of the urban group brought to the hospital within twenty-four hours of the onset of the attack was twice that of the rural patients.

Prognostic Significance of Time Elapsing Between Attack and Hospitalization. From our study early hospitalization following an episode of coronary occlusion seems an important factor favoring survival. This is demonstrated in Eigure 2. Forty-two of the patients whose case records were analyzed were already in the hospital when the myocardial infarction occurred. Twenty-three of them were in the hospital for reasons other than heart disease, eight having recently undergone surgical operations. The remaining nineteen were receiving hospital care for some type of heart disease. The immediate mortality among the group in the hospital at the time of the coronary occlusion was high (74 per cent), probably because the patients comprising this group were already sick and less able to survive the additional cardiac insult.

The patients who were admitted to the hospital within twenty-four hours of the onset of the attack seemed to have a better chance for survival than did those who were admitted between twenty-five and ninety-six hours. This difference is probably significant. Among those admitted ninety-six hours after the attack the immediate mortality was significantly lower, possibly because the most seriously ill patients had already died or because the attack in those who survived to be hospitalized after this length of time was not so severe.

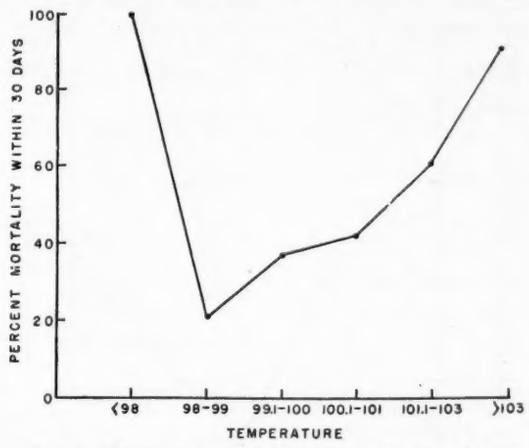

FIG. 3. Temperature with attack and mortality.

Temperature. The degree of temperature elevation during the attack proved to be a helpful prognostic guide. In those cases in which the temperature during the first week was known it was found that the likelihood of an early death increased directly with the degree of temperature elevation. (Fig. 3.) This is in accordance with other reports.[4,5,30,31]

There were six patients whose temperature remained subnormal during the entire period of observation. None survived the immediate attack. Four were moribund or in shock when first seen and died within forty-eight hours. The other two died suddenly on the sixteenth and twenty-first days.

Pulse. Most observers are agreed that a rapid pulse rate associated with acute myocardial infarction indicates a poor prognosis.[4,5,6,32] The prognostic value of a slow pulse with the attack has not been emphasized.

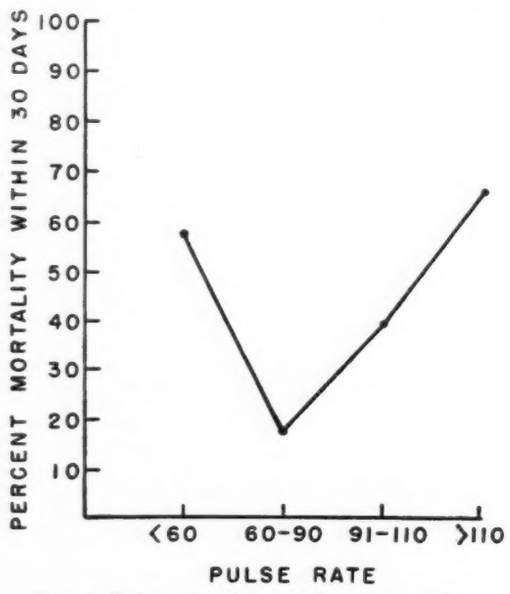

FIG. 4. Pulse rate with attack and mortality.

A pulse rate of more than 90 beats per minute was recorded in over one-half of the patients whose rates shortly after the acute attack were known. In about one-third of the cases the rate was more than 110 beats per minute. The immediate mortality among those whose pulse rate exceeded 110 beats per minute was significantly high. (Fig. 4.) A pulse rate between 60 to 90 beats per minute was associated with low immediate mortality. Bradycardia of less than 60 beats per minute was observed during the first week after the attack in twenty-one patients, over half of whom died within thirty days. Patients with complete auriculoventricular block are not included in this group. It seems that a pulse rate slower than 60 beats per minute or faster than 110 beats per minute during the first few days following the attack is ominous. The three patients with complete auriculoventricular heart block survived the acute episode. Two died within the year of heart disease other than acute infarction. The other is leading an active life seven years later.

Blood Pressure. A fall in blood pressure is considered to be one of the cardinal features of myocardial infarction. This occurred in approximately one-half of the patients in our group. In the series as a whole a fall in blood pressure at the onset of the attack was associated with significantly high mortality. However, when hypertension existed prior to the attack the fall in blood pressure appeared to alter the prognosis but little, if at all, whereas any fall in pressure was of grave portent in the previously normotensive group. (Table VIII.)

TABLE VIII

BLOOD PRESSURE WITHIN TWENTY-FOUR HOURS OF THE ATTACK DIFFERENCE IN PROGNOSTIC IMPORT BETWEEN HYPERTENSIVE AND NORMOTENSIVE PATIENTS

Blood Pressure Behavior	Patients with Hypertension		Patients with Normal Blood Pressure	
	Inci- (per cent)	Immediate Mortality (per cent)	Inci- (per cent)	Immediate Mortality (per cent)
No change	38	31	47	25
Any fall	54	40	43	62*
Less than 50 mm.	15	25	36	64*
50 mm. or more	39	46	7	50
Rise	8	12	10	11
Total	100	35	100	40

* Probably significant

In seventeen patients a rise in blood pressure with the acute attack was observed; fifteen survived. Levine and Rosenbaum[4] reported an immediate rise in blood pressure in ten patients, all of whom survived. However, Chambers[33] reported only one survivor in a group of five similar patients. The elevation of blood pressure which occurs occasionally in myocardial infarction has been attributed to the severity of the pain.[4,6,26] Analysis of the records of the seventeen patients whose blood pressure rose revealed that eight experienced severe,

six moderately severe and one mild pain. One patient experienced no pain during the attack. In one case the record was unsatisfactory for analysis.

Pulse Pressure. A low pulse pressure has been reported by others[4,26] to be an unfavorable prognostic sign. In this series there were thirty-five patients whose pulse pressure fell below 25 mm. Hg at some time following their attack and the mortality rate was 77 per cent. The mortality rate for those whose pulse pressure was maintained above this level was 33 per cent.

TABLE IX
RELATIVE IMMEDIATE MORTALITY OF OBESE, NORMAL AND UNDERWEIGHT PATIENTS

Weight	Incidence (per cent)	Immediate Mortality (per cent)
Obese	33	32
Normal	51	39
Underweight	16	60*

* Probably significant

Weight. The impression has long existed that obese individuals are prone to develop cardiovascular disease.[39,40] One-third of the 240 patients were described as obese while one-sixth were underweight. The immediate mortality of the obese patients was 32 per cent and for the patients of average weight 39 per cent; it was probably significantly higher (60 per cent) for underweight patients. (Table IX.) Seventy-one per cent of the patients who were overweight had hypertension.

Signs Observed Immediately Following Coronary Artery Occlusion. When associated with myocardial infarction the phenomena listed in Table X are usually expressions of the resultant cardiac dysfunction. Our study reveals that the presence of some of them was of grave prognostic significance.

Heart Sounds. Pericardial friction rub, gallop rhythm, "weak" or "poor quality" of heart sounds and arrhythmias are the auscultatory abnormalities commonly associated with myocardial infarction. The incidence and attendant mortality of these and certain other abnormalities are shown in Table XI.

The figures for the incidence of the phenomena listed are within the range established by previous studies.[4,34] Some authors[4,5,30] have stated that gallop rhythm implies poor prognosis. Pericardial friction rub,[4] auricular fibrillation and pulsus alternans[30] have also been considered grave

TABLE X
SIGNS OBSERVED WITH ACUTE ATTACK OF CORONARY ARTERY OCCLUSION WITH INCIDENCE AND ASSOCIATED IMMEDIATE MORTALITY

Signs with Acute Episode	Incidence (per cent)	Mortality (per cent)
Rales*	58	52
Hepatomegaly*	42	50
Cyanosis*	39	61
Ankle edema†	29	53
Venous distention	21	41
Cheyne-Stokes respiration*	16	74
Shock*	14	79
Generalized edema*	11	74
Ascites†	9	64
Jaundice	2	40

* Significant
† Probably significant

TABLE XI
MANIFESTATIONS OF CARDIAC ABNORMALITIES: INCIDENCE AND ASSOCIATED IMMEDIATE MORTALITY

Manifestations of Cardiac Abnormality	Incidence (per cent)	Mortality (per cent)
Weak or poor quality sounds*	44	50
Extrasystoles	28	47
Markedly enlarged heart*	27	55
Gallop rhythm	26	39
Pericardial friction rub	14	39
Auricular fibrillation*	11	65
Pulsus bigeminus	4	70
Pulsus alternans	3	57
Reduplication of first sound	2	20
Thrills	2	60
Diastolic murmur, apex	2	40
Diastolic murmur, apex and base	1	33
Diastolic murmur, base	1	
Auricular flutter	2	
Pulsus paradoxus	2	50

* Significant

signs. In this series neither gallop rhythm nor friction rub appear to have prognostic significance. Levine and Rosenbaum[4] found gallop rhythm was of grave import when the infarct was posterior but of no significance in anterior wall infarctions. In the

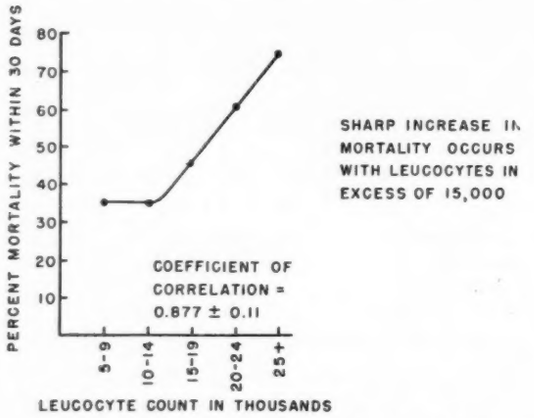

FIG. 5. Leukocytosis and immediate mortality.

study herein reported there was no correlation between gallop rhythm, location of the infarct and mortality. Forty-three of the sixty-one patients in whom gallop rhythm occurred had congestive heart failure. The frequent association of these conditions is well known.[35] The immediate mortality associated with auricular fibrillation, poor quality of the heart sounds and marked cardiac enlargement was significantly high.

Laboratory Data. Laboratory data were for the most part not helpful in indicating prognosis. The chief prognostic aid appeared to be the leukocyte count. There was direct relationship between the degree of leukocytosis accompanying the attack and the patient's chance of survival. Marked leukocytosis indicated a poor immediate outlook. (Fig. 5.) This has been consistently observed by others.[4,5,30] Twelve patients had white blood cell counts of more than 25,000 per cu. mm. Nine died within thirty days. Chambers[5] reported ten similar cases in which none of the patients survived.

The degree of acceleration of the erythrocyte sedimentation rate was of no prognostic importance. Venous pressure, vital capacity and blood circulation time were not determined in a sufficient number of patients to make statistical analysis significant. Cholesterol blood levels were determined in sixty-five of the patients. Thirty-five patients had levels between 150 and 250 mg. per cent. Twenty-five survived the acute episode. A cholesterol level of more than 250 mg. per cent was present in twenty-two patients. Twenty survived. Eight patients had levels below 150 mg. per cent. Four of them survived. The immediate mortality for the patients with either high or low cholesterol levels did not differ significantly from the immediate mortality of the patients with levels in the normal range. Anemia did not seem to be an important factor in the etiology of myocardial infarction. There were only six patients with hemoglobin values of less than 10 Gm. per cent.

Location of Myocardial Infarct. The location of the infarct was determined with accuracy in 139 cases, either by autopsy examination or by electrocardiographic tracings. There were eighty-two infarcts of the anterior wall of the heart and fifty-seven infarcts of the posterior wall. There was no significant difference in the immediate mortality in these two groups. In this series the location of the infarct had no relationship to the frequency of various signs and symptoms accompanying the attacks, to the factors in the past history or to the subsequent course. This is of interest in view of the findings of Levine and Rosenbaum[4] who developed several such relationships. The incidence and mortality figures for our anterior and posterior infarct groups are similar to others in the literature.[11,14,19,23,37]

Digitalis and Quinidine. One hundred fourteen patients with myocardial infarction received digitalis. It was usually given because of the presence of congestive failure or of cardiac arrhythmias. Forty-nine per cent of these patients died within thirty days of the acute attack. This figure is significantly higher than the figure for patients not receiving digitalis. However, the presence of either congestive failure or auricular fibrillation made the prognosis poor and it seems improbable that digitalis

made it worse. We have insufficient data on the effect of digitalis in the absence of congestive failure or arrhythmias to draw conclusions. Others have found it harmful.[11,38]

Twenty-four patients in this series received quinidine at the time of the acute attack because of cardiac arrhythmias. Sixteen (67 per cent) expired within thirty days. Seventy-three patients with cardiac arrhythmias were not treated with quinidine. The immediate mortality among patients in these two groups is not significantly different. Quinidine was used in the hope of preventing cardiac arrhythmias in twenty-one patients. Eight of these patients died within thirty days following the acute attack. Thus quinidine, regardless of the reason for its use in this series, did not appear to affect the prognosis either favorably or unfavorably.

PROGNOSIS AFTER SURVIVING THE ACUTE ATTACK

One hundred forty-three of the two hundred forty patients whose records were analyzed in this study survived the acute attack. In 120 cases it was possible to ascertain roughly the amount of physical activity enjoyed by the survivors. Seventy patients were able to return to usual or somewhat reduced physical activity within a few months following the acute episode. In fifty, chronic invalidism ensued with partial or complete confinement to bed. The survival rates for the group as a whole and for the two subgroups are compared with the rate for a Tennessee population of the same age, race and sex distribution. Figure 6 is a graphic demonstration of the survival curves of the four groups of people as determined by the actuarial method. The graph is plotted with a logarithmic vertical scale so that the slope of a line depends on the mortality rate.

Among the 143 patients who survived the acute attack the mortality rate was higher during a three-year period following the acute episode than for the Tennessee population. Thereafter the mortalities followed about the same pattern. The mortality rate for patients able to resume activity was higher than that of the normal population for the first two years only. The mortality rate for patients completely or partially confined to bed remained significantly high at all times.

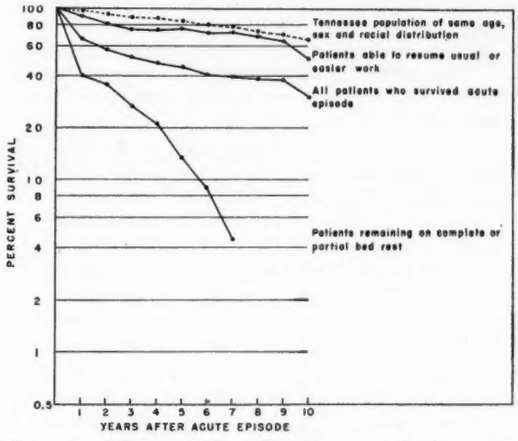

FIG. 6. Myocardial infarction—survival rates; survival curves plotted on a logarithmic scale. The slope of a line segment is a measure of the mortality rate during the period in question. Parallel slopes indicate similar mortality rates. Computed from mortality rates published by U. S. Bureau of the Census.

The ability of patients to return to full or moderate activity following acute heart attacks depends to a large extent on the preservation of adequate cardiac reserve. In addition the patient's general physical condition exclusive of the cardiovascular system must be such as to allow him to be active. We studied the records of the 120 patients whose degree of activity subsequent to the heart attack was known to determine if possible what factor could be shown to be related to a failure to return to work once the acute coronary episode had been survived. Table XII enumerates the conditions which, when present before, during, or after the acute attack, were associated with significant reduction in the patient's chances of resuming activity. It is noteworthy that a history of angina pectoris before the acute attack or its presence afterward was not unfavorable.

COMMENTS

It is obviously important at the time of an acute coronary episode to be able to

determine if possible (1) whether the patient has a good chance of surviving the acute attack and (2) whether having survived the acute episode the condition of the patient's heart will allow for a resumption of some type of activity. The study herein reported was undertaken with the hope of shedding additional light on these questions. We were encouraged in this hope by the fact that there were available records of 240 patients all of whom were carefully studied while under observation in a hospital. The material seemed especially valuable for the purposes of the study because information regarding the subsequent course of events following discharge from the hospital was available in all the patients (143) who survived the acute attack.

TABLE XII
FACTORS SIGNIFICANTLY UNFAVORABLE TO RETURN TO WORK

Factor	Per Cent Able to Return to Work	
	with factor present (per cent)	with factor absent (per cent)
Concomitant diseases		
History of rheumatic fever	17	60
History of peptic ulcer	17	60
Marked arteriosclerosis	44	76
Diabetes mellitus	38	60
Congestive heart failure		
Whether occurring before, during or after acute episode, particularly as manifested by:		
Dyspnea	42	82
Cheyne-Stokes respiration	..	61
Cyanosis	38	66
Ankle edema	22	70
Ascites	14	56
Hepatomegaly	26	76
Râles	33	78
Venous distension	38	64
Markedly enlarged heart	28	66
Urinary casts	31	67
Circulatory collapse		
Auricular fibrillation	31	62
Extrasystoles	43	67
Gallop rhythm	38	66
Miscellaneous		
Systolic murmurs, apex	35	73
Systolic murmurs, base	29	65
Hospitalization for other purposes	..	62

SUMMARY AND CONCLUSIONS

The hospital records of 240 patients with myocardial infarction secondary to either occlusion of a coronary artery or to coronary artery insufficiency were analyzed.

1. Ninety-seven patients (40.4 per cent) died within thirty days following onset of the acute episode.

2. Certain data obtained from the clinical history, physical findings and laboratory investigations were found to be consistently useful in predicting the train of events following development of myocardial infarction:

3. The immediate mortality (thirty days) was high in the presence of any one or more of the following circumstances: (1) A history of congestive heart failure prior to development of the infarct; (2) signs or symptoms of congestive failure or circulatory collapse at the time of the acute attack; (3) absence of pain at the time of the attack; (4) a delay in hospitalization of from more than twenty-four hours to ninety-six hours, inclusively, after the onset of the attack; (5) development of myocardial infarction in a patient already in the hospital; (6) a pulse rate faster than 110 or slower than 60 beats per minute with the attack; (7) a temperature elevation greater than 101°F. or subnormal during the acute attack; (8) cardiac enlargement at the time of the acute attack; (9) presence of auricular fibrillation at the time of the acute attack; (10) leukocytosis in excess of 15,000 with the attack.

4. Follow-up information was obtained concerning the 143 patients who survived the acute attack including data regarding the amount of physical activity engaged in by 120 of these survivors. (1) The following factors were found to influence adversely the likelihood of returning to an active life after surviving an attack of myocardial infarction: occurrence of congestive heart failure either before, during or after the

acute episode; occurrence of circulatory collapse at the time of the acute attack; occurrence of either transient or persistent auricular fibrillation, gallop rhythm or extrasystoles at the time of the acute attack; presence of systolic murmurs at the time of the acute attack; hospitalization for other purposes at the time of the acute attack; a history of either rheumatic fever or peptic ulcer prior to the acute attack and the presence of either advanced arteriosclerosis or diabetes mellitus. (2) The survival rate of those patients who were able to return to some type of useful activity was significantly higher than among those completely or partially confined to bed. This was to be expected when bed rest was mandatory because of diminished cardiac reserve; however, the observation suggests that after a reasonable convalescence, severe restriction of physical activity beyond the requirements imposed by limited cardiac reserve affords little or no protection to the patient who has survived the acute attack.

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Seminars on Antibiotics

Recent Advances in Streptomycin Therapy*

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DURING the few years in which streptomycin has been in clinical usage it has become established as a potent antimicrobial agent of value in the treatment of a large number of infections. Within a relatively short time subsequent to its introduction a large body of information was accumulated in the various clinical studies which fairly well delineated the usefulness of this drug. In the same and correlated studies the important disadvantages attendant upon the use of streptomycin were defined. The advances in our knowledge which have been made since these early studies have not only added extensive confirmation of the earlier findings but have also provided a considerable amount of additional information of value to the clinican. The recent advances have been made along three general lines: (1) the pharmacodynamics of streptomycin in man; (2) studies of a derivative, dihydrostreptomycin, which appears to have certain advantages over the parent compound and (3) further definition of the therapeutic uses of the drug, notably in chronic infections, with surgical procedures or with another antimicrobial agent.

The uses of streptomycin have also been modified to some extent by the introduction of new drugs, chiefly aureomycin and chloramphenicol. It is apparent that these drugs will to some extent replace streptomycin, in that they are active in a number of infections for which streptomycin has previously been the drug of choice. Moreover, they are distinctly preferable from the standpoints of toxicity and the emergence of resistant bacteria during therapy. In some instances it is not yet possible to assess the relative potency of the newer drugs in comparison with streptomycin and opinions at present may require modification in the light of further experience.

It is the purpose of this review to summarize briefly some of the recent advances in the therapeutic use of streptomycin along the lines mentioned above, and to indicate wherever possible the infections for which the newer drugs appear to be preferable.

PHARMACODYNAMICS

The development of chemical methods of the measurement of streptomycin in body fluids[1,2] has led to re-evaluation of some of the pharmacodynamics of the drug in humans. The findings have been in general agreement with the investigations previously reported in which biologic assay methods were utilized.[3,4] The data obtained by the use of the chemical methods, however, not only provide an interesting comparison of methods but also are of sufficient accuracy to permit more detailed analysis than has heretofore been possible. Moreover, they serve to emphasize certain important aspects of the pharmacology of streptomycin which have been recognized previously but which have not appeared to receive adequate consideration in the clinical use of this drug. It seems of interest, therefore, to summarize the main features of the absorption, distribution and excretion of streptomycin as found in these recent studies.[1]

Following a single intramuscular injection of streptomycin in man, the drug is rapidly absorbed and the plasma concentrations reach a peak within an hour. Absorption is sufficiently rapid so that at one hour the plasma concentration may be expected to

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be approximately the same whether the dose has been given intramuscularly or intravenously. The drug is distributed in a percentage of the body weight which approximates that of the extracellular water. With usual doses the values obtained in the blood of humans after a single intramuscular injection of streptomycin are directly related to the dose per unit body weight. In 4.0 to 20 mg. per Kg. doses the rate of fall in serum concentration is proportional to the concentration of the drug in the blood. It is worthy of note that this rate actually is not rapid; and within certain limits, approximately two and one-half to three hours are required for the concentration to fall from any given value to half that value. Excretion of streptomycin is for the most part by way of the kidney. The renal clearance of streptomycin is approximately the same as the glomerular clearance when suitable correction is made for the degree of binding by plasma proteins.[5]

These observations have certain practical implications with regard to the mode of administration of streptomycin. It would appear that little is to be gained by frequent injections of streptomycin as judged by the length of time any given concentration is maintained. Intervals of at least six or eight hours between doses seem permissible, and longer intervals will probably prove generally satisfactory.[6] The recent experiences in the treatment of tuberculosis with single daily doses of streptomycin and with intervals as long as three days between doses lends support to this belief.[7,8] Moreover, as the individual dose is increased, there is a proportional increase in the height of the concentrations attained. A number of experimental observations point to the desirability of obtaining relatively high concentrations in the body. Among these are the fact that the rate of killing of bacteria *in vitro* steadily increases as the concentration of the drug is increased.[9] Another factor to be considered is the recognized occurrence of marked variation in susceptibility of bacteria to streptomycin not only among the various members of one species, but also among the individual members of a single infecting strain.

NEUROTOXICITY

Although some of the foregoing must remain speculative, it has been obvious from the beginning that an important limiting factor in the widespread use of streptomycin is its neurotoxicity. The occurrence of vestibular dysfunction during streptomycin therapy has been a frequent and distressing problem. There is now ample evidence that these neurotoxic reactions occur in a progressively smaller proportion of cases as the daily dose is decreased. While the administration of 3.0 Gm. of streptomycin daily results in vestibular dysfunction in virtually all adults by the end of three weeks of treatment, doses of 1.0 Gm. daily cause this reaction in only approximately 10 to 15 per cent of patients even though given over much longer periods. It is in this lower range of dosage that it seems possible to effect a significant reduction in the incidence of neurotoxicity by administration of streptomycin on the basis of the patient's body weight. In one small series of patients receiving 1.0 Gm. per day[10] the largest patient was actually receiving 13 mg. per Kg. per day while the smallest was receiving 26 mg. per Kg. per day. No neurotoxic manifestations were observed in those patients receiving less than 20 mg. per Kg. per day. This value which was noted in a small series cannot be broadly applied, but the observations serve to emphasize the fact that failure to consider the patient's weight when administering streptomycin may subject him to unnecessary hazard of loss of vestibular function as well as other toxic reactions.

DIHYDROSTREPTOMYCIN

A recent development of considerable interest has been the reports of clinical trials of dihydrostreptomycin, and in particular the studies of its toxicity. This compound is prepared by the catalytic hydrogenation of streptomycin with reduction of the free

aldehyde group to the corresponding alcohol. Dihydrostreptomycin was first studied in the laboratory as early as 1946[11,12] and was then found to have essentially the same antibacterial activity *in vitro* and the same acute toxicity for mice as the parent compound. It thus appeared to offer no obvious advantages over streptomycin and was not investigated further at that time. The first clinical trials of dihydrostreptomycin were made in a small number of patients who developed hypersensitivity to streptomycin and in whom it was found possible to continue therapy without interruption by the use of the dihydro derivative.[10] Subsequently, the drug has been prepared in large amounts for clinical trials which have been in progress since early 1947.[13,14] There is as yet only limited information on the therapeutic effectiveness of dihydrostreptomycin in comparison with streptomycin. From the information available, it appears that dihydrostreptomycin will prove as effective as the parent compound in the same infections and with the same dosage. The derivative possesses no advantage over streptomycin in the problem of the emergence of drug-resistant bacteria during therapy. Micro-organisms resistant to one drug have been found to have a comparable degree of resistance to the other, and there appears to be no difference in the rate at which resistant strains appear during therapy with one or the other drug. The chief interest in dihydrostreptomycin then is in relation to its toxicity.

In general, it may be said that dihydrostreptomycin is qualitatively the same as streptomycin except for its antigenicity, and quantitatively very similar except for its neurotoxicity. The latter difference appears to be sufficiently great; so that if it is confirmed in more extensive studies, it should be a decisive factor in choosing between these two drugs.

The neurotoxic reactions caused by dihydrostreptomycin, both vestibular and auditory, appear to be very similar in character, if not identical, with those caused by the parent compound. It has been the impression of many investigators that the peculiar type of "dizziness" which characterizes the vestibular dysfunction has not been as severe when produced by dihydrostreptomycin, but such observations are difficult to evaluate. Nevertheless, it has been found that dihydrostreptomycin is less toxic than streptomycin for the vestibular apparatus as judged by the dosage required to provoke the reaction both in experimental animals and man. Doses of 60 mg. per Kg. per day or approximately 3.0 Gm. daily in an adult of average size have caused few reactions during the first four weeks of administration; but when the drug is administered for longer periods, the incidence of vestibular damage is increased appreciably. Daily doses of 40 mg. per Kg. or approximately 2.0 Gm. daily in adults have resulted in neurotoxic manifestations only occasionally over periods as long as six to eight weeks. Comparison of these figures with the toxicity of streptomycin clearly indicates that the dihydro derivative has a lower toxicity for the vestibular apparatus.

Whether an appreciable incidence of vestibular dysfunction will occur with doses of 20 mg. per Kg. per day cannot be stated because of the small numbers of patients thus far treated with this dose. From the results with the larger doses, however, one might anticipate that the occurrence of vestibular dysfunction would be rare.

It has been the general experience that nerve-deafness from dihydrostreptomycin toxicity has been no more frequent than that observed with streptomycin and perhaps has been less frequent. In most clinics the occurrence of any significant loss of hearing has not been encountered even with the prolonged administration of 3.0 Gm. of dihydrostreptomycin daily. In some of these patients, however, there has been a 10 to 15 per cent loss of hearing involving the highest tones, and detectable only by audiometric examination. In a recent survey[15] of approximately 250 collected cases (exclusive of two of the three series described below) in which dihydrostreptomycin was administered for one to three months in

doses which ranged from 1 to 3 Gm. daily, there were no instances of hearing loss sufficient to interfere with the patient's hearing normal conversational tones.

In general, the neurotoxicity produced by dihydrostreptomycin also bears a quantitative relationship to dosage. In the original studies of the toxicity of dihydrostreptomycin, however, it was noted and emphasized that both vestibular dysfunction or deafness might first appear at an appreciable interval after the cessation of the chemotherapy. Such instances of the delayed appearance of neurotoxicity have been infrequent and have occurred after the use of unusually high doses in the presence of renal insufficiency.

Nevertheless, three localized outbreaks of neurotoxicity have been encountered with the use of dihydrostreptomycin and it is possible that they may reflect some more serious disadvantage than is now generally believed. The first of these incidents occurred on our own service shortly after the completion of initial studies of dihydrostreptomycin, and after more than one and one-half years of its use here. During the course of a forty-eight hour period five patients who were receiving dihydrostreptomycin in doses of 3.0 Gm. daily suddenly developed severe symptoms of vestibular dysfunction. It would have been unusual in our experience for symptoms of this severity to occur at all in patients receiving dihydrostreptomycin. It was even more unusual that this particular two-day period represented the fourth and fifth days of treatment in one patient, the last of the fourth week in another and periods intermediate in duration in the other three. Thus it appeared that whatever the toxic substance might be, it was probably even more damaging to the vestibular apparatus than streptomycin itself. Every effort was made to determine the cause of this but thus far no definite cause has been ascertained. One factor has been suspected of playing a part, however, and deserves mention although its importance is unknown. It had been the practice to prepare the solutions of dihydrostreptomycin in the pharmacy and send them to the ward for use. Although stamped with an expiration date, it was possible because of a particularly abundant supply at the time as well as some overstocking on the ward that the particular lot of the drug then in use may have been in solution for an unduly long time. Although this procedure was never actually incriminated, the practice was discontinued and no further difficulty of this sort has been encountered in a subsequent period of nine months. Thus although at present this remain an isolated episode, the possibility still exists that dihydrostreptomycin has the potentiality of causing an explosive type of vestibular toxicity in exceptional circumstances.

Moreover, two groups of investigators[16,17] working independently have recently observed the phenomenon of the delayed appearance of deafness following the use of only moderate doses of dihydrostreptomycin. It is not yet established whether the disturbingly higher incidence of the reaction localized to these two clinics is merely a reflection of chance distribution or whether it is possible that certain preparations of dihydrostreptomycin might be more neurotoxic than others. Pending more information, about all that can be said is that dihydrostreptomycin is definitely less neurotoxic than streptomycin, but that the dihydro derivative is by no means devoid of neurotoxicity and its behavior in this respect may be less predictable.

Finally, dihydrostreptomycin has proved to be useful in small numbers of patients who have developed some of the manifestations of hypersensitivity to streptomycin. A small proportion (estimated to be 3 to 5 per cent) of patients who have received streptomycin for several weeks have developed drug fever, asthma or other manifestations of hypersensitivity of sufficient severity to warrant interruption of therapy. In the few instances in which it has been tried, it has been possible to continue the antimicrobial therapy of patients experiencing such reactions by the substitution of dihydrostreptomycin.

In summary, it appears that dihydrostreptomycin has a lesser toxicity than streptomycin for the vestibular apparatus; and if it can be established with certainty that the derivative is the equivalent of streptomycin therapeutically, the difference in toxicity may prove decisive in a choice between the two drugs. The three sharply localized outbreaks of neurotoxicity which have occurred with dihydrostreptomycin are disquieting, and their relationship to the intrinsic toxicity of dihydrostreptomycin itself should be established as quickly as possible. The other toxic reactions to dihydrostreptomycin have been no greater than those caused by streptomycin and the derivative has proved valuable in preventing the interruption of therapy in patients who develop manifestations of hypersensitivity to streptomycin.

THERAPEUTIC USES OF STREPTOMYCIN

The scope of the clinical usefulness of streptomycin was well delineated in the first two years of its use, and the various infections for which it has been proved of value are thoroughly reviewed elsewhere. It is worthy of mention that the first definitive report of the efficacy of streptomycin in plague has appeared within the past two years.[18] More extensive experience in the treatment of Salmonella infections has strengthened the earlier impression that it has little or no value in these infections. Somewhat to the contrary has been the development of the present opinion in relation to treatment of infections caused by Ps. pyocyaneous and B. proteus. There is a prevalent belief based on some of the earlier reports that streptomycin is of little or no value in these infections which arise most commonly in the urinary tract. Nevertheless, a review of the reported cases leads to the conclusion that streptomycin has an impressive effect in a large number of the cases of urinary tract infections caused by these two species. Moreover, in a number of these cases the urinary tract infection was accompanied by bacteremia. In Keefer and Hewitt's monograph[19] nineteen cases of Ps. aeruginosa bacteremia treated with streptomycin are reported. There were nine recoveries and ten deaths. In this same report are included sixteen patients with bacteremia caused by B. proteus who received treatment with streptomycin. Twelve of the sixteen were permanently improved by the therapy and there were four deaths. These results, while far from ideal, serve to emphasize the fact that streptomycin may actually prove highly beneficial in infections of this type which are so refractory to treatment with most of the other antimicrobial agents.

CONCURRENT ADMINISTRATION OF STREPTOMYCIN AND ANOTHER ANTIMICROBIAL DRUG

There is at present an increasing interest in the use of streptomycin administered concurrently with another antimicrobial agent appropriate for the particular infection to be treated. In theory, the effects of such "combined therapy" might be detectable in one of two ways. First, the emergence to predominance of drug-resistant microorganisms might be delayed, and second, the course of the infection might be altered to an extent not observed from the use of streptomycin alone. Either type of result would reflect the simultaneous activity of both antimicrobial drugs.

The demonstration that "combined therapy" exerts a greater effect upon the clinical course of an infection than either drug alone can be made satisfactorily only in relatively "drug-resistant" infections. The favorable results noted by Spink and his associates[20] from the combined use of streptomycin and sulfadiazine in the treatment of brucellosis are an example of this type of demonstration. It should be noted, however, that although this procedure represents a valuable advance in therapy, it has now been largely superseded by the use of aureomycin or chloramphenicol.

A second example of the concurrent administration of two drugs has been the use of streptomycin and penicillin in the treatment of subacute bacterial endocarditis caused by enterococci.[21,22] Within the past

two and a half years the writers have employed this therapy in eight patients with this form of endocarditis which has previously been unusually refractory to attempts at treatment. From the results obtained in this small group of cases there can be little question that the concurrent administration of penicillin and streptomycin provides highly effective therapy. Moreover, the results are obtained without the necessity for using massive doses of penicillin or other measures to attain very high concentrations of penicillin in the body. It cannot be stated with certainty whether the effects observed resulted entirely from the streptomycin, inasmuch as the value of streptomycin alone has not been thoroughly established. From the limited information available, however, it seems likely that the concurrent use of the two drugs is more efficacious than either alone.

Another possible indication for the concurrent administration of streptomycin and penicillin is in the treatment of staphylococcic infections. The diseases caused by these species represent virtually the only situation in which the emergence of penicillin-resistant bacteria might constitute a problem. As a consequence, it is advisable at present to attempt to avoid this threat by the simultaneous administration of two antimicrobial agents.

Combined therapy has been utilized also in a small number of patients with tuberculosis in an attempt to prevent or postpone the emergence of significant numbers of streptomycin-resistant tubercle bacilli. In this infection the consequences of the appearance of resistant organisms are magnified because of the chronic nature of the disease process. To effect even a relatively short delay in the emergence of resistance would therefore be highly desirable. Combined therapy in tuberculosis has been studied both with para-amino-salicylic acid and with one of the sulfones administered at the same time as streptomycin. From studies in the Veterans' Administration it appears that the administration of various sulfones, such as promizole, in conjunction with streptomycin is without influence on the emergence of streptomycin-resistant tubercle bacilli. In contrast, on the basis of preliminary observations by D'Esopo[23] and Karlson[24] and their respective associates, it appears that para-amino-salicylic acid administered along with streptomycin may significantly postpone but does not completely prevent the phenomenon of drug-resistance.

STREPTOMYCIN IN TUBERCULOSIS

It was apparent when streptomycin was first introduced into clinical practice that the greatest field of usefulness for the drug would be in the treatment of tuberculosis. This is particularly the case at present because aureomycin and chloramphenicol are preferable drugs for the treatment of many of the gram-negative bacillary infections which were previously best treated with streptomycin. It has been thoroughly established that streptomycin exerts an impressive effect upon the course of tuberculosis in humans and the changes observed in the various forms of the disease during the first few months of streptomycin therapy are now thoroughly familiar. There is very little information available, however, concerning the late results of therapy when streptomycin has been used in quantity for a sufficient period. Accordingly, brief mention will be made of the late results in the New York Hospital-Cornell study which is now finishing its fourth year.

Miliary and Meningeal Tuberculosis. Since January, 1946, twenty-four patients with either acute generalized hematogenous tuberculosis (i.e., miliary), tuberculous meningitis or both forms of the disease have been treated with streptomycin. Ten patients had hematogenous tuberculosis without the complication of meningitis. Relapse occurred in four of these patients. In one instance the micro-organisms were still sensitive to streptomycin and retreatment was successful. Thus seven of the ten patients with only miliary tuberculosis are alive and only three have died. One of these deaths occurred on the sixteenth day in a patient who had far

advanced pulmonary tuberculosis. The period of observation following the cessation of therapy in this group ranged between fifteen and thirty-six months. The important feature is, however, that all seven patients who were well one year after the completion of therapy for miliary tuberculosis were also well thereafter. In other words, no late relapses were encountered and it appears that recovery from miliary tuberculosis is indeed possible.

A second group of five patients had meningitis which was not associated with hematogenous tuberculosis. In two of the five instances meningitis apparently arose from a focus in the vertebral column. Of these five patients, two are alive and three are dead. The two living patients have survived eighteen and twenty-seven months, respectively, following the cessation of streptomycin therapy.

Ten patients, a number equal to the number with hematogenous disease without meningeal complications, also had meningitis. Thus approximately one-half the patients with generalized hematogenous tuberculosis had meningeal involvement as a complication of their illness at some time during its course. This value is lower than in the Veterans' Administration series, in which approximately two-thirds of the patients with miliary tuberculosis developed meningitis at some time during the course of the infection.[25] In the present series the combined miliary-meningeal type of infection was fatal to all ten patients. Although the numbers are small, the difference between the outcome in this group and the seven of ten recoveries in the group with uncomplicated miliary tuberculosis is striking indeed. It should be noted that in several instances of the combined disease the deaths were apparently not a direct result of the meningitis but were a consequence of the emergence of drug-resistant miliary infections. Nevertheless, our complete helplessness when faced with the combined infection is apparent.

It is of interest in this connection that in the writers' experience the results attained from the antimicrobial therapy of pneumococcic meningitis are vastly different when the meningitis arises apparently as a blood-borne infection in association with pneumococcic pneumonia, than when the meningitis arises as a direct extension from a focus in the sinuses or ears.

The type of pneumococcic meningitis which occurs in association with pneumonia is roughly comparable to tuberculous meningitis complicating miliary tuberculosis, and the pneumococcic meningitis which arises from the paranasal sinus or ear is not unlike the tuberculous meningitis which arises from tuberculosis of a vertebra. The case fatality rate of pneumococcic meningitis which arises in association with pneumonia is extremely high, whereas the meningitis without pneumonia is usually controlled by appropriate therapy. The reason for this difference in prognosis is by no means clear, nor is there any particular reason why similar factors should operate with pneumococcic as with tuberculous infections. It is of considerable interest, however, that the results parallel each other so strikingly in these two infections, both of which are rarely fatal when they involve the lung and so frequently fatal when they involve the central nervous system.

Thus of a total of twenty-four patients with miliary or meningeal tuberculosis, fifteen are dead and nine are alive one to three years after the cessation of antimicrobial therapy. It is probable that the complete remission of illness will be maintained in the nine living patients, for late relapses have not been observed in uncomplicated miliary tuberculosis, and the only two living patients who had meningitis have now survived for a minimum period of two years after completion of therapy. It should be emphasized, however, that all but two of the nine survivors are from the group with miliary tuberculosis who were fortunate enough not to develop meningeal involvement. As at least one-half to two-thirds of the patients with miliary tuberculosis do develop meningeal involvement, it is obvious that the survivors of this total group

of infections represent a highly selected group. If the late follow-up results from the Veterans' Administration series parallel the results from the present series, it could be predicted that out of every 100 patients with miliary tuberculosis, approximately thirty will survive. The great majority of these thirty will be those fortunate individuals in whom meningeal complications do not occur.

Pulmonary Tuberculosis. In the late follow-up of the series of pulmonary cases it is of interest to note the number of patients in whom streptomycin therapy was definitive in the sense that no subsequent collapse therapy was necessary. From one standpoint such a value has little meaning unless it is carefully related to the type of pulmonary lesion for which the antimicrobial therapy was used. It is well recognized, for example, that regardless of the extent of the involvement the number of patients requiring collapse therapy would be appreciably smaller in the presence of predominantly exudative lesions without much necrosis than would be the case with subacute or chronic lesions with large areas of destruction. From a broader standpoint, however, the late over-all results are of significance in that they serve to indicate what is to be expected from the use of streptomycin in those types of pulmonary tuberculosis with which the physician is actually confronted.

During the twenty-three-month period from January, 1946, to November 30, 1947, sixty-seven patients with pulmonary tuberculosis received streptomycin therapy. In general, no patient received chemotherapy if it were anticipated that the pulmonary lesions would regress on bed rest alone. Moreover, collapse therapy was never initiated until it seemed evident that no further improvement from the antimicrobial therapy was to be expected.

One and one-half to three years after these sixty-seven patients had *completed* streptomycin therapy thirteen were dead, thirty-two were alive and well, twenty were alive but still had active pulmonary tuberculosis and two were lost from observation. In seventeen of the thirty-two patients who had recovered, the only antituberculous therapies used were streptomycin and bed rest. In the other fifteen patients who had recovered it had been necessary to institute collapse therapy subsequent to the administration of the streptomycin. Collapse therapy had also been used in eight of the twenty surviving patients whose tuberculosis has persisted in an active state.

Thus in seventeen of the sixty-seven patients with severe or moderately severe pulmonary tuberculosis, streptomycin (and bed rest) had apparently constituted definitive therapy.

The fact that it was necessary to supplement streptomycin therapy with collapse therapy in the other fifteen successfully treated patients does not mean that streptomycin therapy necessarily failed to exert an impressive control of those infections. On the contrary, in many instances in the present series such collapse therapy would never have been possible were it not for the artificial checking of the infection provided by the antimicrobial therapy. As a consequence, it is to be anticipated that more patients will receive collapse therapy rather than fewer as a consequence of the streptomycin therapy. Moreover, as it is now no longer necessary from an experimental standpoint to observe patients for as long as is possible after drug therapy before the institution of collapse, it may be possible to shorten the period of total therapy considerably by the institution of collapse soon after the start of the antimicrobial therapy. Such a practice is becoming increasingly widespread at present, and within a year or two it should be possible to evaluate its benefits with some degree of precision.

EMERGENCE TO PREDOMINANCE OF STREPTOMYCIN-RESISTANT TUBERCLE BACILLI

The relatively long-term results presented above represent what can be accomplished when streptomycin, despite its handicaps, is incorporated into the over-all treatment of tuberculosis. It is well recognized that the principal handicap consists of the fact that

drug-resistant micro-organisms will emerge and become predominant whenever streptomycin therapy is continued for a sufficient period in the presence of unhealed lesions.

The fact that unhealed or persistently active lesions are a necessary factor for drug resistance is not always appreciated. Many internists not directly concerned with the chemotherapy of tuberculosis have gained the impression that regardless of the status of the lesion all the tubercle bacilli within the patient become resistant to the drug when it has been administered for a certain period. Assuming that the genetic explanation of the origin of drug-resistant infections is correct,[26,27] and the available evidence appears to point in this direction, if an infection were receding under drug therapy so that a large number of the bacterial population were being sterilized, it would not be anticipated that the emergence of drug-resistant bacteria would occur in a sufficient number to enable them to become predominant. Consequently, in lesions which are rapidly regressing to the point of arrest, it might be anticipated that the micro-organisms remaining therein would be predominantly sensitive and that a relapse of the lesion many months later should be susceptible to retreatment with streptomycin. From the scattered observations which have been made, such would indeed seem to be the case. Conversely, if a lesion remains active throughout a sufficiently long period of drug therapy, sufficient generations of tubercle bacilli would be constantly occurring so that the possibilities of the emergence to predominance of drug-resistant variants would be very real indeed. It is for this reason that the emergence to predominance of drug-resistant strains of tubercle bacilli is much more of a problem in the treatment of patients with cavities than in the treatment of patients with diffuse nodular lesions.[28,29] It is only when the latter are large or present in great numbers, as in certain cases of miliary tuberculosis, that drug-resistance becomes a problem. Thus, it is presumably not the morphologic arrangement of the lesion in the form of the cavity, but merely the fact that the cavity happens to represent one of the most frequent forms of persistently unhealed lesions that is responsible for the high incidence of drug-resistance in association with cavities.

Effect of Dose on Emergence of Drug-Resistant Tubercle Bacilli. The attempts to prevent or postpone the emergence to predominance of streptomycin-resistant bacteria by the concurrent administration of another drug have already been discussed. Another approach of substantial but limited promise consists in suitable alterations in the time-dose relationships of the streptomycin dosage regimen. This question is intimately interwoven with the question of the *size* of the daily dose of streptomycin which will produce the maximal attainable antimicrobial effect per unit of time.

The 1 Gm. daily dose of streptomycin is virtually free of serious neurotoxicity and undoubtedly produces significant therapeutic effects in all diseases caused by streptomycin-sensitive species of bacteria. It is by no means established, however, that the effects observed on this low dosage represent the maximal attainable effects.

Because of the many familiar variables it is extremely difficult to measure degrees of therapeutic effectiveness from comparison of the clinical courses of patients treated with various quantities of an antimicrobial drug. This difficulty is particularly accentuated in chronic infections such as tuberculosis in which the principal measurement of continued activity consists of the relatively insensitive tool of serial roentgenographic examinations. One reasonably precise type of observation which may be used in such evaluation of proper dosage, however, is an analysis of the pattern of the emergence of drug-resistant strains of micro-organisms in patients treated on various regimens of the drug.

Bacteriologic studies of this type were conducted by the writers in sixty-four patients with pulmonary tuberculosis who were treated on one or the other of two streptomycin regimens. Thirty-three of the patients received 3 Gm. of streptomycin daily and the remaining thirty-one received

1 Gm. of the drug each day. All strains of tubercle bacilli isolated from both groups of patients before treatment were quite sensitive to streptomycin *in vitro*. Moreover, on both the 3.0 Gm. and the 1.0 Gm. regimens highly resistant strains (i.e., not inhibited by 100 micrograms of streptomycin per cc. of medium) appeared during the treatment in approximately the same incidence. The significant difference between the two treatment groups lay entirely in the incidence of strains with an intermediate degree of drug-resistant (i.e., resistant to concentration which ranged between 2 to 100 micrograms of drug per cc. of medium).

On 1 Gm. of streptomycin daily these "intermediate strains" appeared early and their incidence steadily increased. In contrast, on 3 Gm. daily virtually all strains of tubercle bacilli discharged by the patients were either highly resistant or quite sensitive to streptomycin throughout the observation period. In effect the "intermediate" strains observed on the low dosage regimen represented large numbers of tubercle bacilli which could be killed by the administration of 3.0 Gm. of streptomycin but were not killed on the 1 Gm. regimen.

The following interpretation has been made of these observations. The precise degree of drug-resistance which must be attained by the major part of a bacterial population within the body before essentially complete nullification of streptomycin occurs is not known. Nevertheless, when one bacterial cell with increased resistance to streptomycin is born, the effectiveness of the streptomycin therapy of that infection has been compromised by that little bit. When the survival of bacteria of an intermediate degree of resistance is prevented, the curve of antimicrobial activity would persist at a high level until sufficient time had elapsed for the relatively few highly resistant bacteria to multiply to predominance. From clinical experience this period is approximately ninety days. Thus, the curve of drug effectiveness on the high dosage would be high for several months and then fall off relatively sharply. In contrast, when the survival of bacteria of an intermediate degree of drug-resistance is favored, as is the case on 1 Gm. daily, the curve of drug activity would represent more of a slanting diagonal with a steady fall off in activity from week to week. Moreover, the start of the decline in activity would occur soon after the start of streptomycin therapy. It is most unlikely that such a gradual falling off of the effectiveness of streptomycin in pulmonary tuberculosis could be detected by the relatively crude clinical and roentgenologic means currently available.

On the basis of this interpretation of the bacteriologic observations it would seem advisable to adopt one of two alternatives in the streptomycin treatment of each patient with a chronic infection such as tuberculosis. In instances in which the disease constitutes a clear and present danger such as miliary tuberculosis, extensive pneumonias and the like, a large daily dose of streptomycin or dihydrostreptomycin should be used for a period of three or four months. In this situation the eventual nullification of drug activity and some incidence of neurotoxicity would simply be accepted as inevitable.

In those other forms of tuberculosis in which the prognosis without antimicrobial therapy is reasonably good, streptomycin should be used only as an occasional adjunct to the powerful defense mechanisms of the patient by administering the drug once, or at the most twice, each week. In this way some admittedly limited therapeutic benefits can be obtained without continuously providing an environment which favors the survival of tubercle bacilli of intermediate degrees of drug-resistance.

SUMMARY

The recent advances in the use of streptomycin have included: additional studies on its pharmacodynamics in man; further exploration of the relative therapeutic effectiveness of various dosage regimens; and investigations of the value of the concurrent administration of streptomycin with another antimicrobial agent. The neuro-

toxicity of streptomycin and the frequency with which drug-resistant micro-organisms emerge to predominance during therapy continue to be major problems. Relatively small daily doses of streptomycin (20 mg. per Kg.) appropriately adjusted to the patient's weight exert definite therapeutic effects without undue risk of neurotoxicity. It remains to be established, however, that such low doses produce the maximal attainable antimicrobial effect per unit of time. Dihydrostreptomycin is less neurotoxic than the parent compound, but such neurotoxicity as it does produce is less readily predictable. Nevertheless, the dihydro derivative would seem to be preferable at the present time, particularly when relatively intensive therapy is necessary. Encouraging preliminary results have been attained following attempts to prevent or postpone the emergence to predominance of drug-resistant micro-organisms by the use of large daily doses of streptomycin and by the concurrent administration of para-amino-salicylic acid.

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Combined Staff Clinics

Acute Diffuse Glomerulonephritis

THESE are stenotyped reports of combined staff clinics of the College of Physicians and Surgeons, Columbia University, and the Presbyterian Hospital, New York. The clinics, designed to integrate basic mechanisms of disease with problems of diagnosis and treatment, are conducted under the auspices of the Department of Medicine. The reports are edited by Dr. Frederick K. Heath.

DR. STANLEY E. BRADLEY: The clinical pattern of glomerulonephritis and its association with renal pathology was first pointed out by Richard Bright in 1827. Bright recognized that frequently the disease began acutely with hematuria, albuminuria, edema and a "full and hard" pulse, following scarlatina, exposure or intemperate living. He realized that healing often occurred spontaneously and that apparent subsidence might be followed after a long period by reappearance of edema, albuminuria and marked debility leading inevitably to death. The course of glomerulonephritis and the various forms of renal disease in which anasarca and proteinuria occur have since been more accurately defined but Bright's description of the clinical events stands unchallenged. Studies of the microscopic anatomy of the kidney have been successful in showing the site of the lesion in acute nephritis and in marking out the changes that ensue as the disorder becomes chronically active. Unfortunately, little progress has been made in finding specific therapeutic measures to prevent or halt this process.

During the past twenty years important advances in bacteriologic, biochemical and physiologic technics have opened up new approaches to the problems of etiology and mechanism of symptoms. A rational basis for the treatment of the various manifestations of the disease has been achieved by a better understanding of the functional derangements and it is hoped that specific therapy will ultimately arise from the clarification of etiology.

Acute diffuse glomerulonephritis is for the most part a disease of youth. According to Seegal and Lyttle, approximately 70 per cent of cases occur before the age of twenty-one. It is relatively uncommon, making up about 0.5 per cent of medical hospital admissions in the United States. This figure is undoubtedly misleading because only cases of overt illness of sufficient severity to warrant hospitalization are included. As will be brought out later, there is good reason to believe that renal involvement may not be clinically evident or particularly alarming in many instances and the majority of cases are probably never recognized.

Classically, the disorder begins abruptly with the appearance of edema which has a curious tendency to collect about the eyes and over the cheeks although in grosser forms all parts of the body may be involved and fluid may accumulate in the serous cavities. At the same time the urinary output diminishes sharply and the urine becomes grossly bloody. Occasionally, however, hematuria is detectable only by microscopy. Proteinuria is almost always found. In association with these evidences of renal dysfunction and water retention a variable elevation of arterial pressure frequently is observed. These changes persist for one or two weeks and then, in about 90 per cent of children and 60 per cent of adults, slowly clear.

Various combinations and permutations of different types of involvement of the kidney and vascular system may occur and produce a variety of clinical states. In a few individuals the renal functional disturbance may be so profound that uremia develops. Acute diffuse glomerulonephritis may be manifested from the outset as the nephrotic syndrome; it seems likely that the

acute loss of enormous amounts of protein in the urine contributes to depletion of plasma albumin and hypoalbuminemia. In such cases hematuria may be minimal or apparently lacking. Occasionally hypertensive "encephalopathy" or cardiac failure may predominate and present difficult problems of diagnosis and management. Even in the more serious cases the prognosis is favorable and appropriate treatment usually has a gratifyingly successful outcome. Nevertheless, from 5 to 10 per cent of the hospitalized patients fail to respond and die as a result of renal insufficiency, heart failure or disturbances of the central nervous system. In a somewhat larger number the disease persists and becomes chronic.

The most important clue to etiology lies in the fact that an upper respiratory infection nearly always precedes the onset of acute nephritis by one to three weeks. Intensive bacteriologic studies have implicated the hemolytic streptococcus as the most frequent infective agent responsible for this antecedent episode. Furthermore, scarlet fever, erysipelas and other streptococcal diseases are frequently complicated by acute nephritis. Indeed, Lyttle found typical urinary changes by Addis count at some time in the course of scarlet fever in all of a series of fourteen children. These observations strongly suggest that the hemolytic streptococcus is concerned in some manner with the pathogenesis of acute diffuse glomerulonephritis. Dr. David Seegal will discuss this aspect.

Dr. David Seegal: Considerable evidence has accumulated incriminating the hemolytic streptococcus as the chief causative agent of acute glomerulonephritis. Loehlein in 1907 was among the first to point out this relationship and subsequent studies leading to Longcope's comprehensive investigations have lent weight to this opinion.

With Dr. Lyttle and subsequently with Dr. Emily Loeb, we carried out studies on the role of infection in acute nephritis in 116 consecutive patients admitted to the Babies or Presbyterian Hospital from 1932 to 1937. Eighty-two per cent of the group were under thirteen years of age. This series probably represents the characteristic age distribution in acute nephritis. About three-quarters of the patients gave clinical evidence of an antecedent or progressive hemolytic streptococcus infection. The majority of these infections were of the deep or septic variety unlike the mild pharyngitis associated with the onset of rheumatic fever. Although most of the patients entered the hospital many weeks after the onset of an upper respiratory infection, group A hemolytic streptococci were recovered from the pharynx of 71 per cent of the patients studied. It was impossible on bacteriologic evidence, however, to incriminate the hemolytic streptococcus as an etiologic agent in the remaining 29 per cent. It was necessary, therefore, to search for other evidence of prior infection. With the cooperation of Dr. Heidelberger we found that serum precipitins against several hemolytic streptococcus nucleoprotein fractions could be demonstrated in two-thirds of our patients. However, it was only with the introduction of the antistreptolysin test of Todd that we had a tool to gain the information we sought. In our first series of consecutive patients with acute nephritis, studied in 1933, we found that twenty of twenty-two of the serums contained a sufficiently high antistreptolysin titer to indicate a recent hemolytic streptococcus infection. Serial antistreptolysin determinations carried out subsequently on the serums of several hundred consecutive patients with acute nephritis showed evidence of a group A hemolytic streptococcus invasion prior to the onset of the nephritis in at least 94 per cent of the patients. It is of interest that a considerable number of these patients with unmistakable immunologic evidence of hemolytic streptococcus infection had been described on admission to the hospital as having experienced wet feet, influenza, coryza or intestinal catarrh prior to the onset of the nephritis. Although it cannot be denied that acute glomerulonephritis

may be initiated by other agents, the immunologic evidence indicates that the hemolytic streptococcus is by far the chief instigator.

Before leaving the subject of acute nephritis may we call attention to certain immunologic data which we have collected. The height and duration of the abnormal antistreptolysin titer in patients with acute glomerulonephritis appear to be directly related to the severity, persistence or recurrence of the hemolytic streptococcus infection. However, no such relationship is demonstrable between the antistreptolysin response and the severity or duration of the acute attack of nephritis or the tendency to develop chronic nephritis.

Although accurate figures are difficult to obtain, it is generally stated, as Dr. Bradley mentioned, that about 95 per cent of the acute glomerulonephritis in childhood heals whereas only about 60 per cent of the acute nephritis in adults heals. However, the difference in these figures may be more apparent than real since it is often difficult to differentiate between an initial attack of nephritis and an exacerbation of the chronic form of the disease. Our experience would lead us to believe that some reported episodes of acute nephritis in adults represent exacerbations. Since the latter are manifestations of the chronic state, it is not expected that healing will occur.

Many observations have indicated that patients with healed acute glomerulonephritis are remarkably resistant to second attacks. This is of interest since in rheumatic fever, another disease of proven association with the hemolytic streptococcus, recurrence is common. An opportunity was presented to study twenty individuals clinically, bacteriologically and immunologically during the stage of acute glomerulonephritis, throughout a subsequent healed period and following a later infection with a group A hemolytic streptococcus. Eighteen of the twenty patients experiencing an invasive group A hemolytic streptococcus infection, after healing had been established, failed to demonstrate any significant abnormalities by urine analysis. Two of the patients experienced an infection proved to be caused by the hemolytic streptococcus in one individual and presumably caused by that organism in the other. Both developed immediate gross hematuria unaccompanied by significant proteinuria. The urine analyses became negative in four weeks and one week, respectively. Not one of the twenty patients studied has developed the chronic form of glomerulonephritis. The nature of this impressive tissue immunity is not known.

Healing fails to occur in the minority of patients with acute nephritis and at the end of six months a subacute phase of the disease is apparent. Although this disease may ultimately heal in a few members of this group, the majority will experience progressive inflammation and degeneration of renal architecture leading to death within a few years. In children the combination of edema, hypertension and nitrogen retention is common in this stage. The clinical and laboratory picture is unlike the nephrotic phase of glomerulonephritis. Longcope suggested that the transition of acute nephritis into the subacute phase was related to persistence of the hemolytic streptococcus infection. This was an attractive concept in view of the close relationship which had been established between hemolytic streptococcus infection and the onset of acute nephritis. However, our clinical and bacteriologic experiences did not permit this generalization. In the presulfonamide days it was not unusual for us to see patients whose acute nephritis healed completely in the face of persistent and angry forms of hemolytic streptococcus infection. Conversely, in other individuals the subacute form of nephritis would progress inexorably in the absence of demonstrable hemolytic streptococcus infection. It could not be denied, however, that the infection preceding the acute nephritis might have set off a chain of immunologic reactions which served to activate the nephritis.

The mechanism for the maintenance of the chronic state of glomerulonephritis is

unknown. Two points of view prevail with respect to the nature of the disease. The one opinion held by Longcope and Ellis is that the disease arises *de novo* and is not a projection of acute hemorrhagic nephritis. This may be the correct view but it is less attractive to us than a second possibility. We share de Wesselow's opinion that the majority of patients with acute glomerulonephritis are not seen by a physician. It is reasonable to assume that a number of such individuals fail to heal their nephritis. In time they will present the clinical picture of the nephrotic phase of chronic glomerulonephritis which Longcope and Ellis might consider as arising *de novo*.

The velocity of development of chronic nephritis has wide limits and attempts to relate certain portions of the natural history of the disease to episodes of infection have yielded variable results. It has been possible, however, to obtain useful data concerning the relation of infection to the exacerbation in nephritis. We followed sixty-eight patients with chronic glomerulonephritis for one to eight years. Twenty-eight exacerbations of the nephritis were observed in thirteen individuals. All thirteen experienced at least one exacerbation preceded by a group A hemolytic streptococcus infection. Eight of the exacerbations followed infections which could not be proved due to this organism. No exacerbation of chronic glomerulonephritis in this series occurred without concomitant infection and in twenty of twenty-eight times this was a proven hemolytic streptococcus infection.

The latent period between the onset of the infection and the exacerbation was from one to four days in the majority of instances. This latent period, as pointed out by others, is much shorter than that seen between the infection and the onset of acute glomerulonephritis. This difference may be of some aid in differentiating the acute from chronic forms of the disease.

A common effect of exacerbations is to produce a transient decrease in renal function. Ten of thirteen patients in our series exhibited one to four such exacerbations. In six patients no effect on renal function could be demonstrated; four of these six patients, however, experienced other exacerbations in which a transient decrease in renal function occurred. Only one patient developed a permanent decrease in renal function following an exacerbation but the nephritis was in the terminal stage at the time.

Dr. Earle of our group studied the relationship of the serum antistreptolysin titer to the exacerbation in chronic glomerulonephritis and found among other things that when it occurred, the greater the magnitude of the rise in the antistreptolysin titer the greater was the incidence of associated exacerbation in chronic glomerulonephritis. He further found that the exacerbation preceded the onset of the rise in antistreptolysin titer in seven of the eight sufficiently studied episodes.

Apart from overt exacerbations in the course of glomerulonephritis, it is difficult to relate closely the progression of the nephritis to concomitant hemolytic streptococcus infection. Although the carrier state for the hemolytic streptococcus was observed somewhat more frequently in patients with progressive nephritis than in those in the latent stage, the incidence of hemolytic streptococcus infections and exacerbations was similar in both groups. In individual patients a non-progressive phase of the disease would be apparent over a period of years with or without hemolytic streptococcus infection. Subsequently, the velocity of the nephritis would appear to increase in these patients either with or without the presence of demonstrable hemolytic streptococcus infection. It became apparent that a new experimental approach had to be explored to gain information concerning the mechanism of progressive nephritis.

DR. BRADLEY: The evidence set out by Dr. Seegal gives strong support to the view that the hemolytic streptococcus is directly implicated in causing acute nephritis but more crucial evidence is required before we can accept the concept as more than a reasonable hypothesis. It is necessary to

produce the disease experimentally in animals with streptococci and to demonstrate the mechanisms by which these organisms produce renal damage. The experimental production of glomerulonephritis might provide a means of answering the questions raised by Dr. Seegal regarding the factors involved in perpetuating the acute process with the establishment of a chronically active lesion. Dr. Beatrice Seegal will consider these aspects of the problem.

DR. BEATRICE SEEGAL: Attempts to reproduce nephritis in animals by inducing hemolytic streptococcus infection have generally been unsuccessful. For example, Dr. David Seegal and his associates produced a variety of group A hemolytic streptococcus infections in mice, rabbits, dogs, goats and monkeys but never obtained evidence of nephritis. Similar experiments by other investigators have been equally unsuccessful. On the other hand, Doan and his associates have reported that five monkeys of a group receiving intranasal inoculations of both influenza virus and group C hemolytic streptococci developed clinical manifestations of acute nephritis, namely, edema, hypertension and albuminuria. The urinary sediment contained casts and red cells. Two of the animals were sacrificed during the acute disease. Grossly, the kidneys were large and congested. Histologically, there was evidence of tubular damage and the glomeruli showed thickening of the capsular epithelium with occasional leukocytic infiltration.

From the foregoing statements it may be readily understood that the experimental production of nephritis by the technic of producing group A hemolytic streptococcus infection is unsatisfactory. The results obtained in monkeys following group C hemolytic streptococcus infection indicate the possible advantage of using an animal pathogen in such studies.

An experimental technic which employs an immunologic approach does regularly produce an acute and chronic nephritis similar to the disease of man in a number of animal species. Richard Pearce in 1903 prepared nephrotoxic serums (cytotoxins) by immunizing rabbits with dog kidney. The injection into dogs of the resulting rabbit anti-dog-kidney serum produced acute kidney damage in the dog, albuminuria and cylindruria and, at autopsy, histologic evidence of glomerular and tubular damage. In 1920 Wilson and Oliver repeated these observations and obtained more pronounced glomerular lesions than those reported by Pearce. Ten years later Masugi added a most important observation on the natural history of this nephritis. Masugi used both rats and rabbits as test animals. Anti-kidney serums for each species were prepared; rabbits were immunized with the rat kidneys and ducks with the rabbit kidneys. After injection of the specific antiserums into the rats or rabbits, the animals were studied for weeks or months. It was then observed that the initial acute nephritis might be followed by a chronic progressive disease even though no further injection of the anti-kidney serum was given. In other words, the acute nephritis instituted by the nephrotoxic serum was followed by a self-perpetuating disease.

These observations on the production of chronic progressive nephritis have been amply confirmed. Smadel and Farr have given a particularly clear picture of the progress of the disease in rats. Within twenty-four to forty-eight hours following the initial injection of the nephrotoxic serum there is albuminuria and cylindruria and there may also be edema and hypertension. This acute phase lasts several days and is then usually followed by improvement which may progress to healing. Often, however, in the course of weeks or months albuminuria and cylindruria increase, hypertension and nitrogen retention develop, there is a plasma protein deficit and anemia and, finally, months after the injection of the anti-kidney serum, the animals die of renal insufficiency. Histologically, in the early stages there is swelling of the intercapillary substance of the glomerular tuft and tubular degeneration. Later there is scarring of the glomeruli and tubules.

The following interesting physiologic data have been obtained from studies in animals rendered nephritic by cytotoxic serum: (1) In rabbits, Ehrich has reported diuresis and increase in filtration during the first week after the injection of the anti-kidney serum, followed by oliguria on about the eighth day. He reports the lesion as a diffuse cellular proliferation within all the glomeruli. (2) In dogs, Fouts, Corcoran and Page have observed an early increase in the rate of renal blood flow with decreased efficiency of glomerular filtration which they attribute to thickening of the glomerular basement membrane. (3) Smadel and Farr have found that nephritic rats of the Whelan strain maintained on a diet containing 40 per cent protein have a more severe, rapidly progressing disease, whereas those maintained on a diet containing only 5 per cent protein have a less severe disease than do the control nephritic animals maintained on the stock diet containing 18 per cent protein. Nephrotoxic nephritis in the Wistar white rat was uninfluenced by protein in the diet. (4) Smadel and Swift report that the natural history of cytotoxic nephritis in the Long-Evans and Wistar rat is somewhat different from that in the Whelan strain. Rats of the Long-Evans strain show a decrease in clinical signs between the thirtieth and seventieth day after injection of the nephrotoxic serum and then progression to chronic nephritis. The Wistar rats have a less marked acute nephritis and a period of apparent healing before chronic nephritis develops. In the Whelan strain acute nephritis progresses directly to the chronic state. They interpret these observations as indicating an inherited difference in susceptibility to nephrotoxin.

Nephrotoxic nephritis in the rat is relatively organ-specific. Kidney damage does not follow the injection into rats of nonspecific antiserums prepared by immunizing rabbits with such antigens as rat serum, erythrocytes, heart, liver and testicle. However, Dr. Emily Loeb and I have found that the serum of rabbits which have been immunized with rat placenta is nephrotoxic and gives rise to chronic progressive nephritis as well as to abortion. This is significant in view of the association of renal pathology with the toxemias of pregnancy. Intercurrent pregnancy also has a deleterious effect upon the course of chronic nephritis in man.

The mechanism responsible for the development of cytotoxic nephritis naturally excites great interest. Two pieces of evidence suggest that the antibody concerned in producing nephrotoxic nephritis is directed against glomeruli. Pressman and his associates have iodinated the globulin fraction of rabbit anti-rat-kidney serum and anti-mouse-kidney serum with iodine containing tracer amounts of I^{131}. Radioautographs of the tissues from rats or mice injected with this iodinated antibody have demonstrated that the localization of the radioactivity and presumably of the antibody was in the glomeruli of the kidneys. Other evidence to support the importance of antibodies to glomeruli is that furnished by Ferrebee and his associates (personal communication). A method has been developed for obtaining rat kidney glomeruli in relatively pure state. These have proved capable of absorbing the nephrotoxic agent from antisera prepared by immunizing rabbits with the whole rat kidney.

Kay, in an attempt to explain the disease in rabbits, noted that in this animal, in contrast to the rat, there is a latent period of a week before albuminuria develops following the injection of the nephrotoxin, duck anti-rabbit-kidney serum. He suggested that the antibody-bearing foreign antigen (duck immune globulin) was anchored to the kidney by its immune reaction with this organ. Subsequently, after a period of time corresponding to the latent period observed, antibody to duck globulin developed. This in turn reacted with the duck globulin attached to the rabbit's own kidney cells and acute nephritis resulted. Support for this point of view was obtained by giving x-ray treatment to rabbits injected with the nephrotoxin. This prevented the development of rabbit antibody to duck globulin.

It also prevented the development of nephritis.

This explanation for the acute nephrotoxic nephritis in rabbits cannot be used to explain the disease in rats since there is practically no latent period between the injection of nephrotoxic serum and the onset of signs of acute nephritis. In neither animal is the progressive nature of the chronic disease explained. As Smadel and Swift have well stated, it is difficult to believe that the foreign nephrotoxic serum can persist in the rat's body for many months and contribute to the recurrence or progression of renal disease. These authors suggest that both residual scarring of the glomeruli and "excessive or abnormal stresses and strains to which tubules are subjected" may contribute to the evolution of the chronic nephritis. Another explanation, an immunologic explanation, for the chronic nephritis would assume the possibility of auto-antibody production. Once the kidneys have been damaged by the cytotoxins one may conceive that the kidney proteins are sufficiently altered antigenically to stimulate antibody production. These auto-antibodies, in turn, would damage more kidney tissue and thus give rise to more tissue capable of further stimulating the production of damaging antibodies.

If, in the etiology of human nephritis, one is to implicate a mechanism similar to that operating in cytotoxic serum nephritis, it would appear necessary to assume the production of auto-antibodies to kidney tissue in the presence of hemolytic streptococcus infection. Certainly the patient with nephritis has not been injected with antibodies to human kidney and unless he has contrived to produce some of his own there can be no relationship between the pathogenesis of his disease and the cytotoxic nephritis described in experimental animals. Evidence that antibody to kidney tissue may play a role in human nephritis is furnished by Lange and his associates. In the sera of fifty-one nephritics in all stages of the disease circulating antibodies to human kidney were present, as demonstrated by the collodion particle technic in 72.7 per cent. Higher titers and greater incidence of positive reactions were obtained in cases in which patients were tested after the first month of the disease.

Dr. David Seegal and his associates have attempted to demonstrate experimentally that the hemolytic streptococcus is able to render kidney antigenic for the homologous animal species. The kidneys of both rabbits and rats were exposed to cultures of Group A hemolytic streptococci and were then implanted in normal rabbits or rats. In some experiments fresh kidney tissue was added to broth inoculated with the hemolytic streptococcus and incubated twenty-four hours at 37°C. In other experiments young broth cultures were injected into the renal artery of excised kidneys, thus perfusing the kidney with streptococci. In either case the kidney tissue, saturated with hemolytic streptococci, has been implanted in the peritoneum of animals of the same species. Nephritis has not been obtained by this method.

On the other hand, the Caveltis have succeeded in demonstrating the production of auto-antibodies in both rabbits and rats and have obtained nephritis in the latter animal. They injected these animals with homologous kidney ground and suspended with large numbers of *ether-killed* hemolytic streptococci which stimulated the production of auto-antibodies to the kidney tissue. In the case of the rat, this has been followed by the development of chronic nephritis similar in course and disease picture to that which results from the injection of a prepared rabbit anti-rat-kidney serum. This method for obtaining nephritis is apparently beset with difficulties since Humphrey, using an almost identical technic, has been unable to produce the disease.

The implication of these experiments described by the Caveltis is that the hemolytic streptococcus is able to alter the antigenicity of the kidney so that it can induce auto-antibodies which react with the kidney to produce nephritis. The kidney tissue so

injured may stimulate further anti-kidney antibodies which injure more kidney and so establish a self-perpetuating disease. It must be emphasized that there is no direct evidence in support of such an etiology for nephritis in man and certainly arguing by analogy with animal experiments is hazardous. However, irrespective of the relationship between human and animal nephritis the experiments described serve a very useful purpose. A method is at hand which enables the investigator to study the effects of disturbed renal physiology in animals with renal disease closely simulating human chronic nephritis.

DR. BRADLEY: Even though our knowledge of etiology is incomplete, we seem justified in taking the view that acute diffuse glomerulonephritis is precipitated by some disorder of immune mechanisms in streptococcal infections. Such a disorder may well be susceptible to therapeutic and prophylactic attack. The data obtained from investigations of renal pathology and physiology give further support to this belief since they indicate that acute nephritis is primarily inflammatory and that marked changes may be completely reversible.

The focal point of damage appears to lie in the glomerulus. In the more severe cases there is diffuse involvement of nearly all glomeruli with thickening and reduplication of the basement membrane, proliferation and swelling of the capillary endothelium and infiltration with leukocytes so that cellularity increases strikingly. Later the capsular space contains a fibrinous exudate which becomes organized as "crescents" and is responsible for the formation of adhesions between capillary loops and between the tuft and the capsular wall. Despite marked engorgement of the kidney as a whole, the capillary loops are often empty and collapsed. Marked obstructive distortion of capillaries and proliferation of endothelium may contribute to this by preventing adequate perfusion. The tubules, too, are affected but to a much less striking degree. Here and there desquamation of tubular cells may be found and scattered cells appear to be undergoing necrobiosis. Jean Oliver has called attention to inflammatory changes in the interstitial tissue. The subsequent alterations which may occur with progression do not concern us today; it is remarkable, however, that the widespread lesion of acute nephritis may clear altogether leaving no demonstrable residual damage.

On the whole, the derangements of renal function may be correlated quite well with the morphologic abnormalities. The urinary findings conform with the notion that a glomerular capillary lesion results in filtration of larger molecules than normal, thus permitting albumin and even globulins to enter the filtrate in large amounts. The hematuria is easily traceable to capillary bleeding since erythrocytes may be found within the glomeruli. Red cell casts are obviously derived from masses of red cells packed in the lower reaches of the convoluted tubules and in the collecting ducts, following concentration by the tubular reabsorption of water. Likewise, the demonstrable reduction in glomerular filtration rate, measured by inulin or mannitol clearances, may be ascribed to thickening of the glomerular membrane and/or inadequate perfusion of glomeruli. In Table 1 clearance data collected in studies of twelve patients suffering from acute diffuse glomerulonephritis, as soon as possible after onset, show the extent to which filtration may be impaired, confirming earlier work by Earle, Taggart and Shannon. It will be noted that filtration returns to normal or almost normal values with healing, as in M. B. and in L. L. (Fig. 1.)

This *disturbance of filtration* readily accounts for the tendency to retain nitrogenous wastes. Azotemia, varying in severity and affecting all components of the non-protein nitrogen, is closely correlated to the degree of filtration defect, although augmented degradation of protein may play a part in determining the blood levels. The decreased glomerular filtration is associated with a lesser defect in tubular reabsorption and a

glomerulo-tubular imbalance results which causes disproportionate reabsorption of water and salt, thus contributing directly to retention of water and formation of edema.

In addition to disproportionate renal reabsorption of salt and water by the tubules and, in some patients, hypoalbuminemia, less clearly defined factors often contribute to edema formation in acute nephritis. It is evident that the reduction of water output is directly linked to the accumulation of fluid in the tissues; possibly, however, this phenomenon is secondary in nature. The sudden appearance of facial edema without evidence of weight gain is often cited in support of the belief that acute nephritis is part of a widespread capillary disease in which increased capillary permeability results in a loss of protein and water from the blood into the tissue spaces. Many measurements of the protein content of edema fluid appear to bear this out since protein concentrations approaching those of plasma have been reported. However, tissue fluid samples are easily contaminated with plasma from accidentally punctured capillaries. More recent determinations by Stead and others, with refined technics, have yielded lower values, less than 0.4 Gm. per cent, comparable to those obtained for the edema fluid of heart failure. This finding certainly suggests that capillary permeability is not increased but does not constitute conclusive evidence since it depends upon small samples which are taken from areas of gross edema and may not be representative of edema fluid in general. Recent studies in this country and abroad have disclosed

TABLE 1

RENAL FUNCTION IN ACUTE DIFFUSE GLOMERULONEPHRITIS*

Subject	Sex	Age	Glomerular Filtration Rate	Renal Plasma Flow	Filtration Fraction	Extraction Per Cent	Renal Blood Flow	Tm_{pah}	Azotemia	Edema	Blood Pressure	Estimated Days after Onset
M. B.	F	52	17.4	62.6	27.9	....	....	....	Yes	Yes	164/74	7
			59.6	312.6	19.0	....	....	39.9	Yes	Yes	156/95	11
			84.8	406.0	21.2	....	....	53.4	No	Yes	144/84	20
F. C.	M	11	48.0	363.0	13.2	....	....	29.4	Yes	Yes	140/75	10
			34.5	436.0	7.9	82.9	965	29.5	Yes	Yes	124/80	20
M. C.	M	39	....	505.0	....	76.5	1120	....	Yes	Yes	150/90	24
J. S.	F	6	13.8	112.5	12.4	....	....	8.2	Yes	Yes	172/120	10
I. A.	F	25	28.4	327.0	8.7	47.0	932	....	Yes	Yes	145/95	39
M. S.	M	47	67.0	653.0	10.2	76.4	1278	80.9	Yes	Yes	196/104	9
G. M.	F	7	34.0	251.0	13.5	....	....	15.4	Yes	Yes	120/80	14
E. S.	F	14	41.1	405.0	10.4	79.8	824	....	No	Yes	135/105	20
A. S.	F	37	66.6	598.0	11.1	82.6	1226	54.0	Yes	Yes	150/80	26
L. P.	M	52	90.0	500.0	17.5	69.4	1021	60.2	No	No	234/138	49
H. C.	M	47	157.2	1320.0	11.7	100.0	1320	72.2	No	No	100/60	64
T. B.	M	15	62.8	402.5	15.4	94.0	757	....	No	No	108/72	16
Normal Range			100–150	520–800	17–21	89–100	800–1400	65–90				

* These subjects are arranged in order of severity of the disease process as judged upon clinical grounds. The figures were obtained in studies of patients with clear-cut acute diffuse glomerulonephritis at the Evans Memorial Hospital, Boston, Massachusetts, and the Presbyterian Hospital, New York. Each is an average of two or more determinations. Clearance measurements were made according to the methods described at length by H. W. Smith and his co-workers (see Lectures on the Kidney, Lawrence, Kansas, 1943. University of Kansas Press). The PAH extraction was determined by the method described by Bradley (Tr. Josiah Macy, Jr. Conf. on Factors Reg. Blood Pressure, 1). Normal values are taken from these sources. The headings are as follows: Glomerular Filtration Rate, cc. per minute, measured by the mannitol clearance; Effective Renal Plasma Flow, cc. per minute, measured by the PAH clearance; Filtration Fraction, per cent, equal to Glomerular Filtration Rate/Renal Plasma Flow; Extraction per cent, renal PAH extraction; Renal Blood Flow, cc. per minute, equal to Renal Plasma Flow/Extraction per cent x 1—hematocrit; and Tm_{pah}, maximal tubular excretion of PAH, mg. per minute.

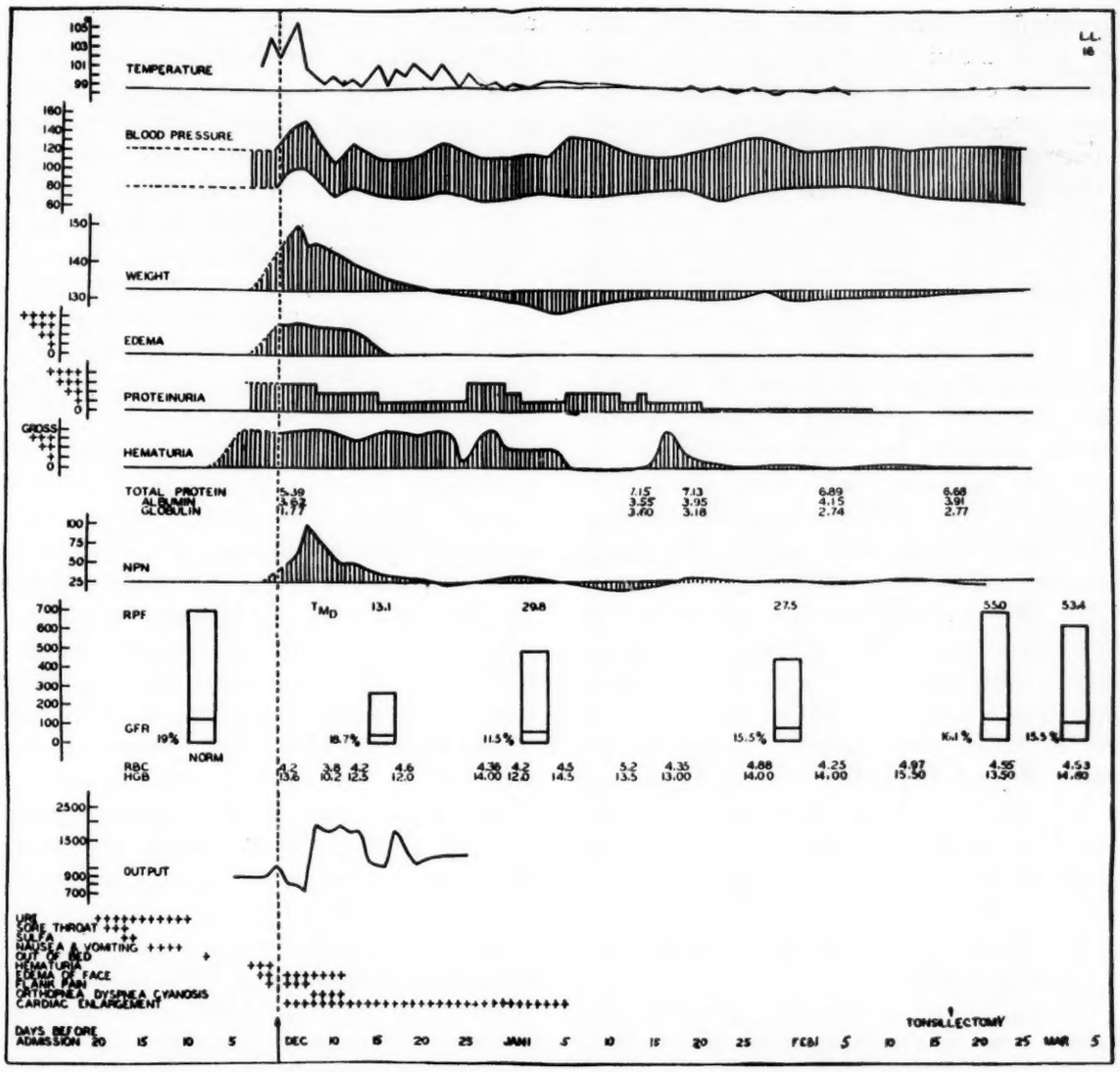

FIG. 1. Clinical course in acute diffuse glomerulonephritis. L. L., a seventeen year old white boy, complained of grossly bloody urine, severe flank pain, weight gain, facial edema and fever of three days' duration. Twenty days prior to admission to the hospital he suddenly became very ill with an upper respiratory infection. He remained in bed for almost two weeks. The body temperature was elevated for four days after hospitalization and then fell abruptly to normal in association with the sudden development of signs of congestive heart failure, including orthopnea, dyspnea and cyanosis. This episode was preceded by a rapid elevation in blood pressure, weight and serum NPN. Digitalization and oxygen therapy were followed by relief of symptoms, by a diuresis and a fall in NPN and blood pressure. The body weight returned to normal less rapidly and the edema slowly cleared. At this time there was a marked reduction in the renal function, including glomerular filtration rate and effective renal plasma flow. The filtration fraction was normal. The maximal tubular excretion of diodrast was also greatly reduced. With recovery, the proteinuria and hematuria slowly cleared, the heart size and electrocardiogram returned to normal and the kidney function gradually improved. Recovery appeared to be complete three months after onset, following removal of chronically infected tonsils. Even at this time, however, the filtration fraction and the filtration rate were significantly reduced.

an apparent increase in plasma volume early in the course of acute nephritis indicating an expansion of the extracellular water as a whole, with coincidental edema.

In many instances heart failure is another important contributing factor in the accumulation of salt and water. Arterial hypertension is but one cause of cardiac failure in acute glomerulonephritis and growing evidence indicates that failure may occur when elevation in blood pressure is but slight or absent. Enlargement of the heart occurs not

infrequently during acute nephritis and Dr. John Dean has reported three cases from this clinic in which it persisted for many months in the absence of significant hypertension. Electrocardiographic abnormalities are encountered at some time during the course of many cases, from 60 to 90 per cent in different series. Rubin and Rapoport and other workers have stressed the frequency with which T_1 is inverted or low in association with depression of ST_1. Reciprocal changes are found in the third lead. Clockwise deviation of Wilson's ventricular gradient has been reported by La Due and Ashman. Since these effects are correlated with cardiac enlargement rather than hypertension, they suggest that rapid dilatation of the heart might be a causative factor. Most investigators have failed to find distinctive pathologic changes in heart muscle although Gore and Saphir have described serous myocarditis in sixteen of one hundred sixty patients dying in the course of acute nephritis. Possibly expansion of the plasma volume operates in this instance, as Stead has suggested, to throw an added strain upon the myocardium (which may be affected adversely in other ways by the disease), precipitating the rapid onset of decompensation.

Certainly one frequently observes the sudden onset of symptoms and signs of congestive failure some time after the appearance of peripheral edema. Such an instance is illustrated by L. L. (Fig. 1), a boy of seventeen in whom edema, hematuria, proteinuria and azotemia were observed at least one week prior to the rapid development of orthopnea, dyspnea and cyanosis, cardiac enlargement and pulmonary edema. Digitalization and oxygen therapy were followed by improvement including a fall in the blood pressure and diuresis. The heart size and electrocardiogram returned to normal much more slowly despite the early correction of blood pressure levels. This sequence suggests the priority of water retention and hypervolemia in the chain of events, serving to focus attention upon the kidney as the chief source of difficulty. In addition, it is evident that heart failure contributed to the impairment of renal function in this case since the blood nonprotein nitrogen concentration rose sharply with the onset of failure and fell slowly toward normal with recovery. Perhaps a superimposed disturbance of the renal circulation accounts for this.

The *renal blood flow* may be measured in acute nephritis as the p-aminohippurate (PAH) clearance corrected by the values for the renal PAH extraction and arterial hematocrit. The extraction of PAH is determined by measuring the PAH concentration in both peripheral arterial or venous blood and renal venous blood obtained from the left renal vein by catheter. The difference between these values divided by the figure for PAH concentration in arterial blood yields a value for the percentage of PAH removed by the kidney from the blood perfusing it. Corrected values for renal blood flow obtained in nine patients by this method are tabulated in Table 1. All were at the upper limits of normal or slightly in excess of normal, denoting a relative or absolute hyperemia of the kidney. This finding is consistent with inflammation and may cast light upon the occasional complaint of flank or back pain which may be throbbing in nature and sufficiently severe to require the use of analgesic agents. In the more severe cases with marked oliguria or anuria the blood flow is probably greatly reduced as a result of obstruction to flow through glomerular capillaries and increased intrarenal tension. Very low diodrast or PAH clearances (effective renal plasma flow), (M. B. and J. S., Table 1; L. L., Fig. 1) which are very difficult to explain in any other way are found in such cases. Even so the reduction in effective renal plasma flow is much less than that in glomerular filtration rate. Hence, the filtration fraction, or percentage of plasma filtered during passage through the kidney, is nearly always reduced below normal. (Table 1.)

The PAH extraction was found to be depressed below the normal range of 89 to

100 per cent in every instance but two (H. C. and T. B.) who had recovered completely according to the clinical evidence. This phenomenon may be interpreted as indicating either arteriovenous shunting of blood or perfusion of damaged tubular tissue. The fact that the maximal tubular excretion of diodrast (L. L., Fig. 1) or PAH (Table 1) is usually reduced favors the latter explanation. Despite the relatively slight anatomic change in tubular cells it is apparent that significant functional alterations have occurred.

Arterial hypertension was observed in most of the cases reported here, regardless of the presence of renal hyperemia relative to the mass of functioning tubular tissue. It is impossible to say whether the change in renal blood flow corresponded to the change in blood pressure since control values were obviously impossible to obtain. There is little evidence that vasoconstriction occurred in the kidney. The cause of hypertension in acute nephritis remains unexplained and insufficient evidence is at hand to warrant speculation. Certainly the various complications of hypertension may have a further detrimental effect upon renal function.

The convulsive seizures and other neurologic disturbances which may have serious consequences in patients with acute nephritis are believed to arise as a result of hypertensive cerebrovascular disease. These manifestations are clearly correlated with the severity of the arterial hypertension and they resemble the "encephalopathic episodes" observed in the course of essential hypertension. Whether hemorrhage, edema or possibly small thromboses are chiefly responsible remains disputed.

Hematologic disorders are occasionally present. In a few patients a severe bleeding tendency will give rise to hemorrhage into the skin, serous cavities, bowel or urinary tract. No satisfactory explanation for this phenomenon has been advanced. Anemia may develop in patients with more severe forms of acute nephritis but is much more common in association with advanced renal failure in the chronic form of the disease. According to recent work by Emerson, both increased blood destruction and impaired blood formation are involved.

In this clinic we have attempted to point out the paths along which progress has been made in clarifying the basic mechanisms of change in acute diffuse glomerulonephritis. Perhaps one of these will prove to be the way to a more complete understanding and more effective therapy of the disease. For the present, treatment is symptomatic and supportive according to principles that Dr. Loeb has agreed to outline briefly for us.

DR. ROBERT F. LOEB: In the patient exhibiting mild acute glomerulonephritis without hypertension, edema or nitrogen retention, no specific therapy is indicated. In the presence of significant hypoalbuminemia or overt edema, intake of sodium salts should be sharply restricted. In fulminating cases exhibiting hypertension and edema associated with marked oliguria it is probably well to restrict fluid intake to the amount excreted by the kidneys plus that lost through insensible perspiration, about 1,200 cc. During this period, which rarely exceeds a few days, it is a good plan to conserve body protein by incorporating 100 to 150 Gm. of carbohydrate in the diet and to exclude all sodium salts from the diet and infusions. Congestive heart failure should be treated by conventional methods.

In the presence of overt streptococcal infection penicillin should be employed although, as indicated by Dr. Seegal, cure of the streptococcal infection probably has little influence *per se* on the course of the nephritis.

STUDENT: How long should the patient be kept in bed?

DR. LOEB: Bed rest should be continued as long as hypertension, heart failure or edema persist. It might be desirable to keep the patients at rest until all the urinary abnormalities have disappeared but unfortunately this is not feasible since albuminuria and hematuria may continue for many months.

STUDENT: What about diuretics?

DR. LOEB: Diuretics have no place in the management of acute glomerulonephritis.

STUDENT: Does potassium poisoning occur in the acute phase of glomerulonephritis?

DR. LOEB: It is probably rare.

STUDENT: Will you comment on the management of convulsions?

DR. LOEB: The management of convulsions consists of sedation, including perhaps the intravenous or intramuscular administration of magnesium sulfate. Lumbar puncture usually does not give convincingly beneficial results.

SUMMARY

DR. FREDERICK K. HEATH: In this clinic emphasis was placed on the relationship of the group A hemolytic streptococcus to glomerulonephritis, certain immunologic mechanisms which might be operative therein, and the pathologic physiology of the acute disease.

Acute glomerulonephritis begins ordinarily one to three weeks following an upper respiratory infection when some combination of the clinical symptoms of hematuria, proteinuria, edema and hypertension appears. The infection is more apt to be deep-seated than superficial although this is not invariable and areas other than the upper respiratory tract may be the site, e.g., wound infections, erysipelas. Throat cultures which are obviously taken when the infection may have subsided are positive for the hemolytic streptococcus in 70 to 80 per cent of cases. Serum precipitins to streptococcus nucleoprotein fractions are found in a proportionate number of cases but antistreptolysin titers give a still higher percentage of positives, being elevated significantly in 90 per cent of cases. The degree of antistreptolysin titer elevation is correlated with the severity of the streptococcus infection and not with the severity of the nephritis. In exacerbations of chronic nephritis, on the other hand, there does appear to be a correlation between the severity of the nephritis and the magnitude of the antistreptolysin titer. Children are more commonly involved than adults and perhaps the majority of cases in either group never come to medical attention. Over 90 per cent of children heal acute nephritis and thereafter remain immune but only about 60 per cent of adults achieve this favorable outcome.

Individuals with chronic nephritis show evidence of hemolytic streptococcus infection prior to an exacerbation in about 70 per cent of cases. Here the time interval between infection and nephritis is greatly reduced, usually being one to four days. Often there is a demonstrable decrease in renal function with exacerbations but this may be only transient or may not be clinically measurable at all. Aside from this, the factors which make for the development of the chronic disease and determine its velocity are not well understood. There is no relationship between continuing infection and progressive nephritis.

In this dilemma the possibility of auto-antibodies has been raised. The production of nephritis, both acute and chronic, in small animals by the use of nephrotoxic sera (anti-kidney or anti-placental) is well established. In monkeys, after a mixture of group C hemolytic streptococcus plus influenza virus was given intranasally, nephritis has been produced; in no animals has nephritis followed the administration of group A hemolytic streptococci. Recently, however, following injection with a mixture of ether-killed hemolytic streptococci and ground kidney, chronic nephritis and auto-antibodies have been demonstrated in the rat. While there is no implication that a similar process exists in human nephritis, the analogy suggests that the streptococcus might so change the kidney that it serves as an antigen to produce auto-antibodies. These in turn react with the kidney to produce nephritis; the damaged kidney again stimulates more auto-antibodies producing further nephritis. In this way a chronic progressive disease might ensue.

The pathologic process of acute nephritis involves chiefly the glomeruli and to a lesser extent the tubules and interstitial tissue. Hematuria, proteinuria and reduction in

glomerular filtration rate are all explained by the glomerular involvement. Nitrogen retention results from decreased filtration. The tubules are able to handle the reduced glomerular filtrate relatively more effectively with a consequent retention of water and salt. Hypervolemia, low serum albumin and possible increase in capillary permeability all favor edema formation. Cardiac failure when present may contribute to this cycle as it may in part be precipitated by it. Hypertension is not essential for the cardiac enlargement and, like the anemia, remains unexplained; both tend to accentuate the renal and cardiac abnormalities.

Renal blood flow is in the normal range as might be expected with the hyperemia of inflammation. Renal extraction is reduced probably because of tubular damage. The reduction in renal plasma flow is often not as marked as that in glomerular filtration rate, hence, the filtration fraction is uniformly decreased. Table 1 illustrates these findings.

Clinico-pathologic Conference

Chronic Pleurisy and Peritonitis*

STENOGRAPHIC reports, edited by Robert J. Glaser, M.D. and David E. Smith, M.D., of weekly clinico-pathologic conferences held in the Barnes Hospital, are published in each issue of the Journal. These conferences are participated in jointly by members of the Departments of Internal Medicine and Pathology of the Washington University School of Medicine and by Junior and Senior medical students.

S. B., (History No. 114547), a white, married accountant, forty-four years of age, entered the Barnes Hospital for the first time on May 29, 1944, complaining of stiffness and swelling of the neck. The family history was irrelevant. The patient had had a chronic morning cough productive of thick white sputum. He had also experienced frequent, spontaneous nosebleeds and on a number of occasions had had abdominal cramping relieved by the passage of flatus. Otherwise his general health had been good. Seven weeks before entry the patient developed a painful left lower tooth which was extracted. Two days later his temperature rose slightly and he noted swelling of the left side of the neck extending down to the left anterior chest. Although over the course of ten days the swelling subsided and the patient became symptom-free, he was admitted to the hospital for study.

At the time of entry his temperature was 36.7°C., pulse 72, respirations 18 and blood pressure 120/80. The patient appeared well. No generalized glandular enlargement was noted. There was a congenital defect in the right retina. Examination of the neck, chest and heart was normal. The liver edge was palpable 2 cm. below the right costal margin on deep inspiration and the spleen could be felt 4 cm. below the left costal margin. The remainder of the physical examination was negative.

Laboratory findings, including a complete blood count, urinalysis, stool examination, blood Kahn test, blood amylase, circulation time and chest roentgenogram, were within normal limits. The venous pressure in the arm was 205 mm. of saline and in the femoral vein, 145 mm. of saline.

The patient left the hospital on June 1, 1944, without a definitive diagnosis having been made. He re-entered the hospital on April 21, 1945. He had been well in the interval until two months before admission when there was an onset of gradual weight loss, vague abdominal pain and mild dyspnea on exertion. His symptoms continued, and he consulted his private physician who noted signs of fluid in the left chest and referred the patient to the hospital.

Physical examination revealed a lymph node in the left supraclavicular fossa measuring 2 by 2 cm. Signs of fluid in the left chest were apparent. The remainder of the physical examination was not remarkable. Routine laboratory studies were normal. Many sputum smears for acid-fast organisms were negative. Chest films revealed encapsulated fluid in the left pleural cavity; some of the fluid apparently was in the interlobar fissure.

Soon after admission a thoracentesis was performed, and 1,000 cc. of blood-tinged fluid were removed. The fluid had a specific gravity of 1.018. It was inoculated into a guinea pig which showed no pathologic lesions at autopsy six weeks later. Cell blocks made from pleural fluid revealed many large multinucleated cells extremely suggestive of Dorothy Reed cells; a presumptive diagnosis of Hodgkin's disease was suggested. Bronchograms were normal. The patient left the hospital on May 18, 1945, and subsequently was given twelve roentgen ray treatments to the left chest.

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He felt quite well until two months before his third admission when he developed a dull aching pain in the left lower chest which was aggravated by heavy lifting, twisting his trunk and lying on his left side but not by coughing or deep breathing. The patient had a mild chronic cough which was productive of a moderate amount of mucoid sputum and he complained of abdominal discomfort characterized by sharp cutting pains in the left upper quadrant. There was also some lower abdominal cramping which he attributed to constipation. During the interim between admissions he had lost no weight.

When he was admitted on December 2, 1947, his temperature was 36.5°C., pulse 78, respirations 20 and blood pressure 125/70. The significant physical findings included dullness to percussion, diminished tactile fremitus, diminished breath sounds and a few crepitant rales over the left lower lung field. The remainder of the physical findings were unchanged from those recorded earlier. Numerous laboratory studies were all negative except for the chest film which showed signs of old pleurisy at the left base and left apex. There was a questionable small amount of fluid in the left pleural cavity but because of overlying shadows the left lower lung field could not be adequately visualized. A gastrointestinal series and a cholecystogram were within normal limits. Bronchoscopy was performed but no abnormal findings were noted in the tracheobronchial tree. A diagnosis of chronic pleurisy was made and the patient was discharged on December 11, 1947.

His cough decreased as did the discomfort in the left chest. About three weeks after discharge, however, the chest pain recurred and was more severe than it had been previously; the patient was admitted for the fourth time on January 9, 1948. Physical findings and laboratory data were no different from those noted previously. Soon after admission the patient was subjected to an exploratory thoracotomy under general anesthesia. A section of the seventh rib was removed and a pocket containing fluid was entered. About 50 cc. of clear, yellow fluid were aspirated and penicillin was instilled into the cavity. The pleura was biopsied; microscopic examination revealed only the changes of chronic inflammation. No tumor cells were seen. The patient had an uneventful postoperative course and during his entire admission, as on the two previous ones, he was afebrile. He was discharged on January 22, 1948, with a diagnosis of pleural effusion, etiology unknown.

He continued to have intermittent pain in his left chest. In February, 1948, marked localized epigastric pain, which came on particularly during meals, appeared. It was unassociated with any other gastrointestinal symptoms or signs until his abdomen began to swell. When he saw his physician three weeks before his fifth admission, signs of ascites were detected and on July 3, 1945, he re-entered the hospital.

At that time his temperature was 37°C., pulse 100, respirations 20 and blood pressure 120/80. The patient now appeared chronically ill. Examination of the chest was as previously noted. The abdomen was distended, but no signs of fluid were demonstrable. The liver extended 6 cm. below the right costal margin. Bleeding hemorrhoids were present; otherwise, the physical examination was not remarkable. Laboratory findings revealed a normal blood count except for a slight left shift in the differential. Numerous liver function studies were normal. Intravenous pyelograms were negative. Sigmoidoscopy was performed and no abnormalities were found. The abdominal bloating and cramping gradually decreased and disappeared but the patient continued to have pain in his left chest. An enlarged lymph node in the right anterior cervical region was removed but on microscopic section showed only chronic lymphadenitis. The patient was discharged unimproved on July 17, 1948.

He continued to have constant dull pain in the left lower chest and occasional sharp

transient pain in the same area. His appetite became poor and he lost 5 pounds. The hemorrhoids became large and bled considerably. A persistent itching eruption appeared over the anterior chest and arms. The patient was re-admitted on August 12, 1948, for nitrogen mustard therapy.

At the time of entry the temperature was 36.5/c., pulse 84, respirations 12 and blood pressure 120/80. Signs over the left lung were attributed to thickened pleura. The abdomen was tense, with signs of ascites. No other new findings were observed.

The red blood cell count was 3,650,000 with 9.8 Gm. of hemoglobin. The white cell count was 5,050, the differential showing 3 per cent stab forms and 72 per cent segmented forms. The urinalysis, thymol turbidity test, cephalin-cholesterol flocculation test, total and fractional proteins, serum phosphorus and alkaline phosphatase were all within normal limits. The patient received 6 mg. of nitrogen mustard intravenously on four successive days and on the fifth day abdominal paracentesis was performed. Twenty-four hundred cc. of grossly bloody fluid were removed. The fluid had a specific gravity of 1.018, a total protein of 4.5 Gm. per cent and there were 2,800,000 red cells per cc. Cultures of the ascitic fluid were negative for bacteria and fungi; guinea pig inoculation also was negative. Cell block sections showed numerous endothelial cells but no tumor cells. After paracentesis the patient was noted to have both a large liver and a large spleen. During his first few hospital days the temperature was 38°c.; following paracentesis it rose to 39°c. and then fell to normal. The patient left the hospital on August 20, 1948.

During the month which elapsed between his sixth and seventh admissions the patient continued to complain of anorexia, weight loss, pain in his left chest, constant dull aching in the upper abdomen and generalized cramping abdominal pains and distention. In addition he was troubled with marked constipation, bowel movements occurring only once every five to seven days. He had occasional mild chills.

He entered the hospital for the last time on September 20, 1948, at which time his temperature was 36.6°c., pulse 92, respirations 20 and blood pressure 110/70. The patient was poorly nourished and appeared chronically ill. The scars from his previous operative procedures were healed. The skin was quite pallid. There was no generalized enlargement of the lymph nodes. Examination of the upper respiratory tract was within normal limits. Examination of the chest revealed limitation of motion on the left side where diminished tactile fremitus dullness and distant breath sounds were noted. The heart was not enlarged. A grade II, blowing, systolic murmur was heard over the pulmonic area. The abdomen was distended and quite tense. No organs or masses could be felt. Small hemorrhoids were noted. No edema was present.

The laboratory findings were as follows: Red cells, 3,900,000; hemoglobin, 9.8 Gm.; white cells, 6,100; differential count: normal. Urinalysis: negative. Stool examination: negative. Electrocardiogram: tendency to right axis deviation.

Following admission to the hospital the patient was given several blood transfusions and an exploratory laparotomy was performed. When the peritoneum was opened, bloody fluid was visible. Diffuse adhesive peritonitis was the most striking finding; all of the viscera were matted together, so much so that neither the spleen nor the liver could be palpated. Two sections of tissue were removed from the parietal peritoneum which felt nodular. Tissue was also removed from the mesentery of the small intestine. Microscopic sections subsequently showed only the changes of chronic inflammation. Sections were also taken from retroperitoneal lymph nodes. Microscopic study of these revealed complete obliteration of the architectural pattern with prominent fibrosis and relatively acellular connective tissue. Plasma cells were abundant and a few eosinophiles were seen. The most common cell was large with a vesicular nucleus and pink cytoplasm. At times rather prominent nucleoli were

seen and in some areas it was thought that the cells resembled Reed-Sternberg cells, but no definite diagnosis could be made. The patient withstood the operative procedure well. He received the usual supportive measures including parenteral fluids and blood. His appetite remained poor. After recovery from the surgical procedure he received 7,000 roentgen units to the abdomen. Despite transfusions, moderate anemia persisted. Following x-ray therapy the red blood cell count was 2,880,000, the hemoglobin 7.6 Gm. and the white cells, 2,150. The differential was normal. Although there was inadequate intake of food, the patient's condition for several weeks following operation showed little change. The serum proteins remained normal until early in December, several months after admission, when they were found to be 4 Gm. per cent. The albumin was 2.7 Gm. per cent and the globulin 1.8 Gm. per cent. Blood chlorides were 94 mEq./L. These studies were made about the time that the patient developed pitting edema of his thighs and ankles. Anorexia persisted and frequent spells of vomiting occurred. On December 15th the patient had a sudden onset of sharp pain in the right chest posteriorly, associated with shortness of breath and increased cough. There was no fever. Physical examination revealed dullness and absent breath sounds over the right base posteriorly and a loud friction rub was audible over the lower half of the right chest. A chest film revealed an area of triangular infiltration which was interpreted as pneumonia. Because of the possibility of pulmonary infarct, however, Dicumarol therapy was instituted. The patient was also given antibiotics. Despite these measures he became weak and irrational. The pulse became feeble and his blood pressure fell to 95/85. His respirations slowed and he expired quietly on December 18, 1948.

CLINICAL DISCUSSION

DR. HARRY L. ALEXANDER: This case is most complicated and we shall certainly not be able to discuss all of the interesting aspects involved. If the assumption is made that this long illness was a result of a single disease, it will be perhaps profitable to inquire what disease is compatible with such a clinical course. This patient was ill for four and one-half years and at times the disease process, if indeed it was a single one, involved the pleura, lymph nodes, liver, spleen and peritoneum. It seems likely that the tooth extraction and apparent secondary infection which occasioned his original admission were not of significance in relation to the clinical picture as a whole. It was of interest, however, that at the time of his first admission, splenomegaly and hepatomegaly were noted. At the time of the second admission a pleural effusion was present. Dr. Flance, can you suggest a disease which may have started with a pleural effusion and gone on to the clinical manifestations which were exhibited here?

DR. I. JEROME FLANCE: Pleural effusion, either inflammatory or malignant, associated with splenomegaly is compatible with a number of diseases which involve the reticulo-endothelial system. Included in that group are such infections as tuberculosis and histoplasmosis; among malignant diseases, certainly the lymphomas merit serious consideration.

DR. ALEXANDER: Would you seriously consider tuberculosis as the etiologic factor here?

DR. FLANCE: In retrospect, the fact that this patient was afebrile during most of his illness and the fact that except after nitrogen mustard and x-ray he had a normal blood count without monocytosis seem to me to exclude tuberculosis.

DR. ALEXANDER: Guinea pigs were inoculated with pleural and abdominal fluid from this patient on several occasions, and none of these animals died from tuberculosis. Would you comment on those results in relation to exclusion of tuberculosis as a possible diagnosis?

DR. FLANCE: I do not believe that a negative guinea pig inoculation completely excludes the diagnosis of tuberculosis, nor

do I think that the fact that no tubercles were found in microscopic sections from the involved areas excludes the diagnosis.

DR. ALEXANDER: But you would exclude the diagnosis on the basis that the patient was essentially afebrile with a normal blood count for most of the duration of his illness?

DR. FLANCE: Yes, I think that in this particular situation both of those findings are most important.

DR. ALEXANDER: Dr. Skilling, you saw this patient. Would you tell us what your thoughts were in regard to the possible diagnosis when the patient first consulted you?

DR. DAVID M. SKILLING: I saw him for the first time just before his second admission to this hospital. As was noted he had a bloody pleural effusion, and I was rather impressed by cells which strongly suggested Reed-Sternberg cells. However, in the absence of lymph node involvement I was loath to accept the diagnosis of Hodgkin's disease on the basis of cell block studies alone. No cells suggestive of any other malignant disease were observed. The negative guinea pig studies seemed to me to constitute strong evidence against a diagnosis of tuberculosis, and I agree with Dr. Flance that the absence of fever, likewise, was not consistent with a diagnosis of tuberculosis in this particular situation. I was unwilling to exclude that diagnosis completely, however, until I had followed him for many months.

DR. ALEXANDER: Is localized pleural effusion common in Hodgkin's disease?

DR. SKILLING: I have never seen it without evidence of hilar adenopathy or involvement of lymph nodes at some other site.

DR. ALEXANDER: What is your opinion on that subject, Dr. Reinhard?

DR. EDWARD H. REINHARD: I would agree with Dr. Skilling. Bloody pleural effusion is certainly not the rule in Hodgkin's disease although I suppose it may occur.

DR. BRUCE D. KENAMORE: Did this man have a tuberculin test?

DR. ALEXANDER: Yes, he had a negative tuberculin test. Dr. Moore, do you believe that the patient may have had Hodgkin's disease:

DR. CARL V. MOORE: If we did not have the numerous negative biopsy reports and if we were not aware that this man failed to show any response to nitrogen mustard, I think that Hodgkin's disease would be an apt diagnosis. In view of these observations, however, I think one may discard the diagnosis of Hodgkin's disease.

DR. ALEXANDER: What disease would you suggest in its place?

DR. CARL MOORE: I am unable to offer a diagnosis. I think, as Dr. Flance pointed out, that one of the granulomas should be considered, but I cannot be specific.

DR. ALEXANDER: Dr. Reinhard, are you willing to discard the diagnosis of Hodgkin's disease? I believe you saw the lymph node sections.

DR. REINHARD: I saw at least one of them and did not think the microscopic picture suggested Hodgkin's disease. In addition there were a number of clinical features which would be most unusual in Hodgkin's disease. The patient never had fever except on rare occasions and he never had significant lymphadenopathy. Furthermore, there was no leukocytosis and no eosinophilia. I administered nitrogen mustard to this patient as a therapeutic test. We thought we were justified in so doing, in that had he had Hodgkin's disease we probably would have helped him. He made no response whatsoever and I agree that Hodgkin's disease does not seem to merit further consideration.

DR. ALEXANDER: Do patients with Hodgkin's disease always respond to nitrogen mustard therapy?

DR. REINHARD: Certainly in a great majority of patients there is a good response provided the patient has not received nitrogen mustard previously. The improvement may be of extremely brief duration, but pain and anorexia particularly are benefited. Fever, which so often accompanies Hodgkin's disease, is also usually controlled by nitrogen mustard therapy.

DR. ALEXANDER: May not a patient have Hodgkin's disease without exhibiting peripheral lymphadenopathy?

DR. REINHARD: That is possible, but unlikely. It seems to me that in a patient such as this man, in whom tuberculosis and Hodgkin's disease can be fairly well ruled out, one has to consider fungus infections seriously. I distinctly remember a patient presented at a conference here some years ago in whom at autopsy there was diffuse actinomycosis with abscesses in the spleen. The infection had extended up through the diaphragm and had given rise to a left pleural effusion. Such a sequence of events may have occurred here.

DR. HENRY A. SCHROEDER: There are certain features in this case which are not unlike those described in polyserositis. Usually, however, the pericardium is involved in polyserositis and there is certainly no evidence that such involvement was present here.

DR. ALEXANDER: To me, one of the most impressive features about this case was the adhesive peritonitis. Dr. Kenamore, what explanation do you have for this finding?

DR. KENAMORE: It seems to me that the most likely possibilities, namely, tuberculosis and carcinomatosis, have been excluded. I think it is fair to say that the latter has been fairly well excluded on the basis of the repeated biopsy specimens, cell blocks and exploration. Lymphoma may also give rise to this clinical picture.

DR. ALEXANDER: Dr. Scheff, what is your opinion?

DR. HAROLD SCHEFF: I would agree with Dr. Kenamore.

DR. ALEXANDER: Dr. Ackerman, you saw these biopsy sections when they were sent through the surgical pathology laboratory.

DR. LAUREN V. ACKERMAN: I was asked to review a section from this rather complicated case and I am afraid that I was not able to be of much help. I would agree that there was no evidence of tumor or of Hodgkin's disease, either in the lymph node or in the pleura. The findings were chiefly those of fibrosis. The section from the pleural fluid showed large numbers of what I interpreted as mesothelial cells; I could not convince myself that any of them were true Reed-Sternberg cells. I have never found it possible to make a diagnosis of Hodgkin's disease on the basis of examination of cell blocks made from either pleural or peritoneal fluid. I have, however, in several instances made a diagnosis of lymphosarcoma. I think that the latter diagnosis is less difficult to make on cell block specimens. A section of the pleura taken at the time of thoracotomy showed a great deal of fibrous tissue and evidence of chronic inflammation. There were large cells present which remotely suggested Reed-Sternberg cells, but I am afraid that one could not identify them as such. Several of the sections taken at the time of the abdominal exploration were most interesting. I should like to point out some of the difficulties involved in attempting to make a definitive diagnosis from cell blocks of peritoneal fluid. Figure 1 is an example of proliferation of the peritoneum which occurred in a patient with cirrhosis of the liver. I suspected carcinoma when I saw this section and subsequently when the patient died he was found to have cirrhosis without carcinoma. Figure 2 is a section of a cell block of normal peritoneal fluid in which the pseudo-acini certainly suggest tumor. Mesothelial cells may be multinucleated and may even have mitotic figures. It may be most difficult to distinguish them from carcinoma cells.

DR. THOMAS H. HUNTER: Is it not possible that this patient had a mesothelioma?

DR. ACKERMAN: I do not believe that there is any way of ruling that diagnosis in or out.

DR. HUNTER: A patient with mesothelioma may have a very prolonged course as this man did. I saw a similar patient at the Presbyterian Hospital in New York who was a most baffling diagnostic problem for a rather long period of time. He, too, had involvement of both the pleural space and peritoneum.

DR. ALEXANDER: If this patient had had carcinomatosis which involved many of the abdominal viscera, would you not have expected that biopsy from an involved area would have shown the lesion?

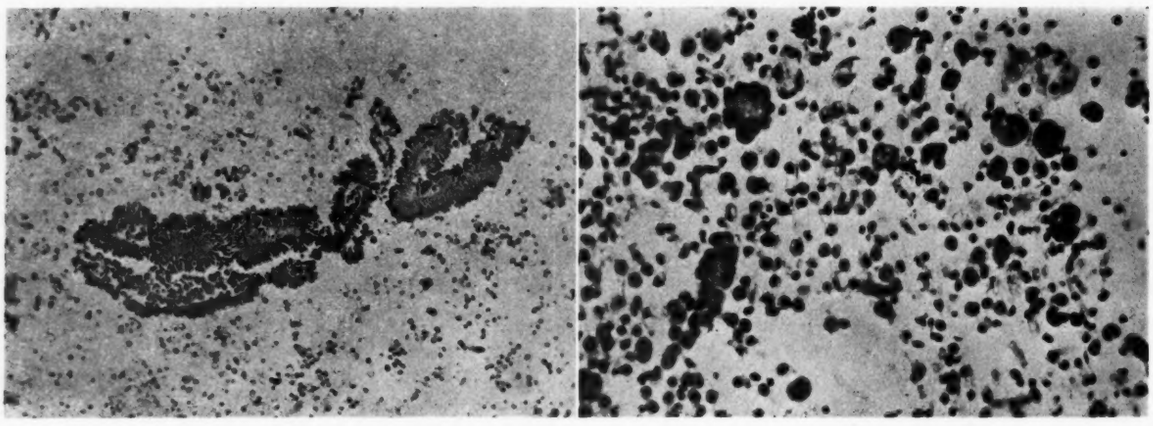

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FIG. 1. Photomicrograph of a paraffin section made from peritoneal fluid; note the large pseudo-acini. This section was thought to be carcinoma by several pathologists. At postmortem examination the patient had cirrhosis of the liver; there was considerable peritoneal reaction with proliferation of mesothelial cells but no carcinoma.

FIG. 2. Photomicrograph of paraffin section of normal peritoneal fluid; numerous pseudo-acini are present. Note the very large cells and the pleomorphism.

DR. ACKERMAN: When this patient was explored, the gross appearance did not suggest carcinomatosis to me nor did I find anything in the biopsy that suggested that diagnosis. At the time of operation carcinoma of the pancreas had been considered but such a clinical course as this man exhibited would be most unusual.

DR. REINHARD: It seems to me that the possibility of fungus infection still remains here.

DR. ALEXANDER: I should think that if this had been a fungus infection the causative organism would have been demonstrated sometime during the intensive study.

DR. SKILLING: At the time pleural fluid was originally removed from this man's chest a thorough search was made for fungi but none was found.

DR. ALEXANDER: In summary, I think that we would all agree that there is no obvious diagnosis in this case. It seems unlikely that either tuberculosis or carcinoma was responsible and Hodgkin's disease also seems unlikely. Fungus infection has been suggested but no evidence has been secured to substantiate it. Finally, mesothelioma has been proposed. I believe we shall have to depend on the pathologists to demonstrate the nature of the lesion which produced this most complicated and unusual clinical picture.

Clinical Diagnosis. ? Fungus infection of unknown type; ? mesothelioma.

PATHOLOGIC DISCUSSION

DR. CLARENCE PICKARD: The right pleural cavity contained 800 cc. of clear greenish-yellow fluid. There was a small focus of fibrin on the posterior surface of the right lung. The left pleural cavity (Fig. 3) was completely obliterated from apex to diaphragm by an extremely firm, dense mass of light tan fibrous tissue, varying from 2 to 60 mm. in thickness, which penetrated into the lung substance and was so firmly attached to the chest wall that it could not be stripped away. The lung within this hard shell was very firm to palpation. A ropy, mucopurulent secretion was present in the bronchi.

All the abdominal viscera were matted together by massive diffuse adhesions. The parietal peritoneum was 1 to 3 mm. thick and was studded with multiple, miliary, firm, gray nodules as much as 3 or 4 mm. in diameter. The visceral peritoneum and mesentery likewise were thickened and nodular. (Fig. 4.)

A small, firm, gray nodule, 2 cm. in diameter, was present in the body of the pancreas and extended into the posterior wall of the stomach. There was a large, soft, spongy mass lying anteriorly between

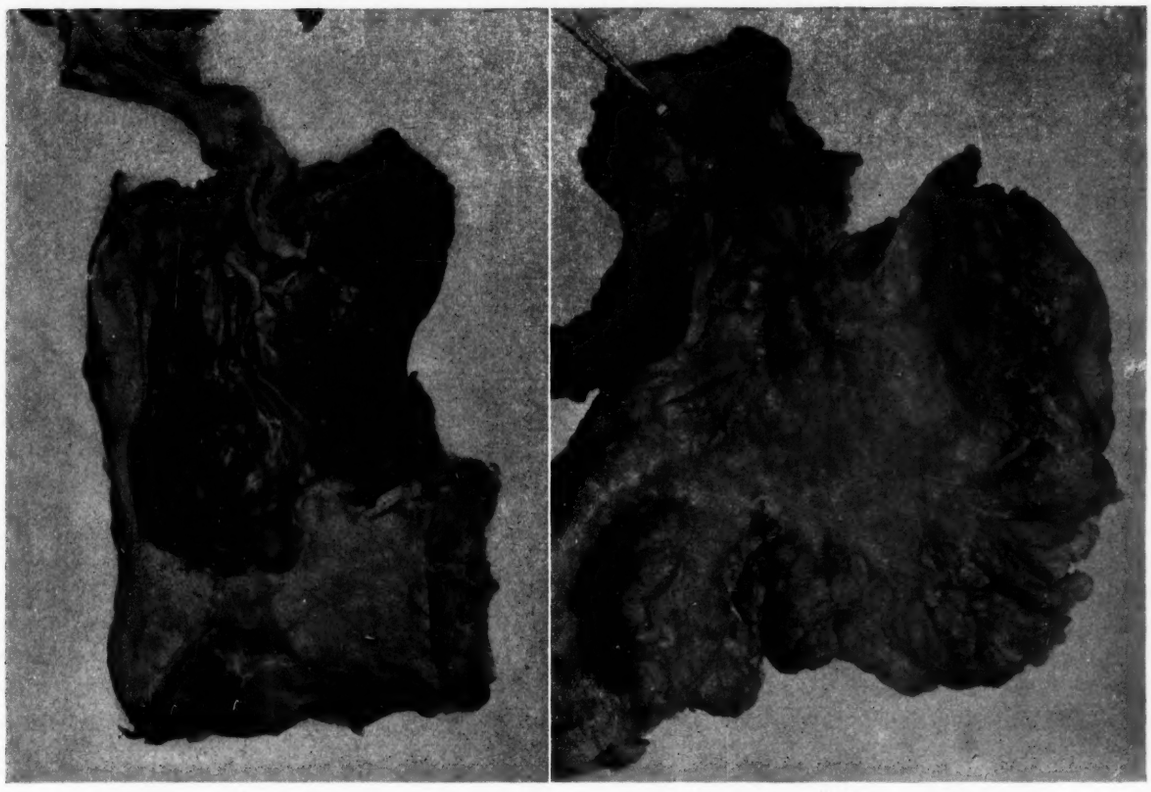

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FIG. 3. Photograph of the pleura and lung showing the thickening of the pleura due to the mesothelioma. The underlying lung is collapsed.

FIG. 4. Massive thickening of the mesentery due to involvement by the mesothelioma.

the stomach and colon. All of these structures were firmly fixed together. The mucosa of the entire gastrointestinal tract was intact.

Other significant findings were generalized serous atrophy of fat and a small heart with brown flabby myocardium.

DR. ROBERT A. MOORE: The gross observations were not too helpful in establishing a diagnosis. In our preliminary examination we were impressed by the tumor mass in what appeared to be the substance of the pancreas, by the nodules over the surface of the peritoneum and by the apparent involvement of some of the lymph nodes about the head of the pancreas. These and the large mass in the upper abdomen were certainly suggestive of the diagnosis of carcinoma of the pancreas. Such a tumor is one of the more common intra-abdominal carcinomas producing widespread metastases to the peritoneum inasmuch as the pancreas itself is immediately adjacent to the peritoneum and cells apparently are shed into the peritoneal cavity and become implanted over its surface. The principal findings that were not in keeping with that diagnosis were the changes within the left pleural cavity which we interpreted at the time of the gross examination as chronic pleurisy with fibrous thickening of the pleura. We did not associate these two findings and consequently we made two separate diagnoses: carcinoma of the pancreas with metastases to the peritoneal cavity and to the regional lymph nodes, and fibrous thickening of the pleura and obliteration of the left pleural cavity.

One objection to the diagnosis of pancreatic carcinoma arose. Although it is quite possible for carcinoma of the pancreas to metastasize in the way it was presumed that this lesion did—that is, without metastases to the liver or to the thoracic cavity—it is not common. A second diag-

nostic possibility was therefore considered, namely, a tumor whose primary site was the peritoneal surface, the so-called mesothelioma; however, the mass in the substance of the pancreas appeared to be of such a character that we were led to believe that it probably represented the primary lesion. All of the other organs were carefully searched, particularly the lung, because carcinoma of the bronchus may lead to changes similar to those observed in the left pleural cavity. Many of the tumors described in the literature and accepted over a period of years as mesotheliomas of the pleura have been proved by more careful examination to be primary bronchogenic carcinomas which have spread into the pleural space. There was one specimen in point in the museum at Western Reserve University which for fifteen or twenty years was used as an example of mesothelioma of the pleura. One day Dr. Karsner was studying carcinoma of the bronchus and in the course of his investigation he opened several of the bronchi in that particular specimen which had not been previously opened. One of them was found to be the site of a classical primary carcinoma of the bronchus. It is therefore necessary to establish the diagnosis of mesothelioma on the basis of both positive and negative evidence. In other words, it must be shown that a tumor has not, so far as one can determine, arisen in some organ and then spread to involve the pleural or peritoneal surface. Second, the histologic characteristics of the tumor must be consistent with what one would expect if the tumor had originated from mesothelial cells.

The photomicrographs from the autopsy material illustrate the histologic character of the tumor in this case. Figure 5 is from a nodule in the peritoneal cavity which Dr. Pickard described. There are large polygonal or round cells that are oriented to one another, in that they are lined up in flat sheets. They do not form glandular spaces and many of the sheets of cells have a connective tissue core as if the tumor was papillary in type. Papillary forms of mesotheliomas have been described both in the peritoneum and pleura. Figure 6 is another section at higher magnification. The cells have an abundant quantity of cytoplasm and large anaplastic nuclei with prominent nucleoli. In some sites the tumor forms sheets of cells with opposing surfaces flattened against the adjacent cells. Such an arrangement is one which is characteristic of a mesothelioma. At an even higher magnification (Fig. 7) the multinucleated character of some of the cells is apparent. Some of the multinucleated cells have overlapping nuclei such as are frequently seen in the Hodgkin's type of giant cell.

A differential histologic point in the diagnosis of mesothelioma is the absence of mucin within the cells. Not all carcinomas contain mucin in terms of gross or general microscopic appearance, but it is most unusual for a carcinoma originating from a mucin-secreting organ, such as bronchus, pancreas or the gastrointestinal tract, not to contain small globules of mucin in some cells. A stain for mucin in these preparations showed absolutely none in any of the cells.

In sections from the pleura the histologic picture was essentially similar. Figure 8 illustrates the dense connective tissue, which I suspect was related to the radiation therapy, and a buried mass of tumor which has undergone necrosis in its avascular center. Figure 9 is a higher magnification of a field in that nodule in which the cells, aside from vacuolation of the cytoplasm, show essentially the same characteristics as the malignant cells in the peritoneum. The last photograph (Fig. 10) is of a section of a tracheobronchial lymph node which was not recognized in the gross as containing tumor. In some of the sinusoids, however, are small groups of cells identical with those in the pleura and in the peritoneum.

In sections of the pancreas the lobules of parenchyma were distinctly separated from the nodules of tumor and there was no transition from normal cells to tumor cells as is characteristic of primary carcinomas

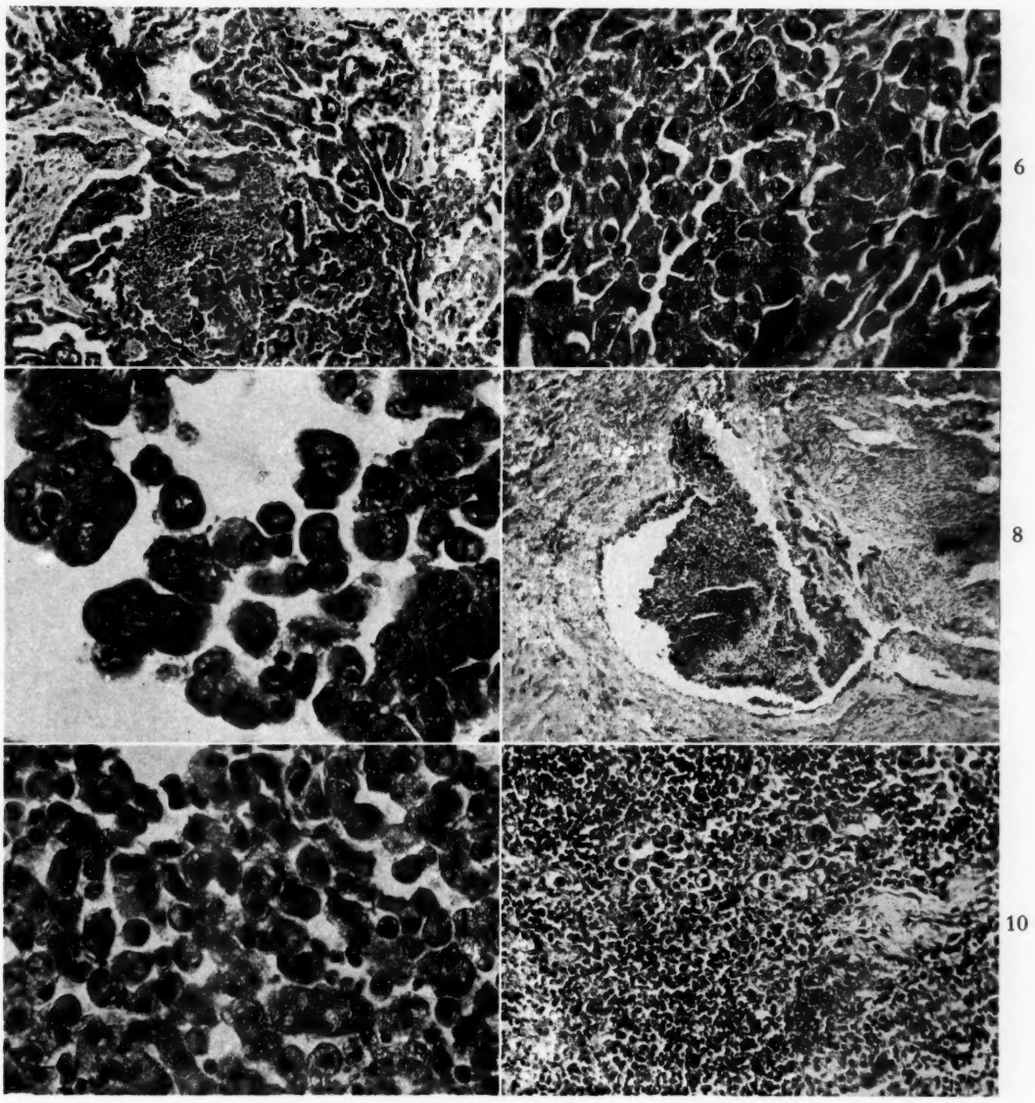

FIG. 5. Section of a peritoneal nodule in which the cells of the mesothelioma are arranged in a papillary pattern.
FIG. 6. A nodule of tumor from the peritoneum in which the mesothelioma is of a solid character.
FIG. 7. Multinucleation, large nucleoli, abundant cytoplasm and anaplastic nuclei in the cells of the peritoneal tumor.
FIG. 8. A nodule of partially necrotic mesothelioma buried in dense fibrous tissue from the left pleural cavity.
FIG. 9. Cellular details of the mesothelioma of the pleura which are essentially identical with the peritoneal tumor.
FIG. 10. Isolated metastatic cells of the mesothelioma in a tracheobronchial lymph node.

of that organ. By careful re-examination of the gross specimen we have also been convinced the tumor was not within but rather around the head of the pancreas.

From the microscopic study then there is evidence which enables us to come to a definitive diagnosis. First, the histologic characteristics of this tumor are those of a mesothelioma and second, the only alternate possibility—that of a primary carcinoma—has been excluded by the absence of characteristic findings of pancreatic carcinoma. Therefore, the final diagnosis is mesothelioma involving both the peritoneal and pleural surfaces.

Dr. Hunter's comment about a case of mesothelioma involving two mesothelial surfaces was most informative; we had been

unable to find reference to such a case. I think a final and essentially unanswerable problem in this case is whether the tumor arose in the pleura and spread to the peritoneum, whether it was a primary tumor of the peritoneum which spread through the diaphragm to the left pleura or finally whether it was a tumor which arose simultaneously in two serous surfaces. The long clinical history is consistent with the general observation that these tumors do not grow very rapidly.

DR. ALEXANDER: Were you surprised that the diagnosis was not revealed when sections of the biopsies of the pleura and peritoneum were studied?

DR. ROBERT MOORE: No, I was not surprised; even at the time of autopsy the pleura was mostly dense fibrous tissue. In the section of pleura which we studied, for example, I demonstrated one nodule of tumor; in that same section there was one other nodule one-quarter the size of the first. That constituted the total amount of tumor in one section. The chance omission of tumor in a given biopsy specimen is obviously quite possible, particularly in a case such as this.

DR. ACKERMAN: When I was told the final diagnosis in this case, I reviewed the biopsy material with increased interest. I can say that the first biopsy of the pleura showed nothing but fibrosis. It is unfortunately true that unless a biopsy is taken from the right area it is very difficult to make a diagnosis of mesothelioma in the presence of minimal foci of proliferation of mesothelium. I think that it would have been perfectly possible to make the diagnosis here if the biopsy had been taken from a different area. The cell blocks of both the pleural fluid and peritoneal fluid undoubtedly contained tumor cells which we interpreted merely as stimulated or proliferating mesothelial cells.

DR. ROBERT MOORE: The point is this: in hindsight there are tumor cells in some of the material, but any pathologist who made the diagnosis of a mesothelioma on the basis of the biopsy material could not have supported it. There were no cells not entirely consistent with hyperplasia of the peritoneal surface in response to the presence of a fluid over a long period of time.

DR. HUNTER: The patient I had in mind repeatedly accumulated blood-stained fluid in his pleural and abdominal cavities. There was one outstanding feature of that fluid: it was extremely viscous and had the consistency of cold honey. It was found to contain large amounts of hyaluronic acid. As a matter of fact it took about an hour to remove 2 or 3 hundred cc. of the fluid. Later hyaluronidase was injected directly into his peritoneal cavity and then the fluid was removed with ease.

DR. ACKERMAN: Dr. Hunter's observation is very interesting because these tumors are essentially similar to tumors which arise within the joints and which also produce large amounts of hyaluronic acid.[1] In regard to mesotheliomias several excellent papers may be consulted for further information.[2–5]

Final Anatomic Diagnoses. Mesothelioma involving the pleural surfaces of the left thoracic cavity with complete obliteration of the pleural space, and involving the peritoneum with extension into the pancreas, posterior wall of the stomach and wall of the transverse colon; metastatic mesothelioma in the left tracheobronchial and bronchopulmonary lymph nodes and in the mesenteric lymph nodes; atelectasis of the left lung, moderate.

Acknowledgment: The photographs were made by the Department of Illustration, Washington University School of Medicine, St. Louis, Mo.

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Special Feature

American Federation for Clinical Research

ABSTRACTS OF PAPERS PRESENTED AT THE NATIONAL MEETING HELD IN ATLANTIC CITY
MAY 3, 1949

RENAL CLEARANCE OF CREATININE BY PATIENTS WITH MUSCULAR DISEASE. *Frank H. Tyler, M.D., Salt Lake City, Utah.* (From the Department of Medicine, University of Utah.)

In recent years it has become obvious as the result of a number of studies that the renal clearance of endogenous creatinine is a good measure of glomerular filtration rate in normal individuals and in most patients with nephritis. When this method was used to study the creatine-creatinine metabolism of patients with progressive muscular dystrophy, strikingly low filtration rates were found. When the standard inulin and p-aminohippurate clearances were measured, it was found that the glomerular filtration rate (Cl In), the renal plasma flow (Cl PAH) and the filtration fractions were normal. Simultaneous creatinine clearances, however, ranged from 30 to 70 per cent of the inulin clearance values. Furthermore, the reduction in creatinine clearance showed good correlation with the severity of muscular wasting. The same observation in a less striking degree was made in two patients who had hyperthyroidism with muscular atrophy.

The explanation of this apparent discrepancy is not clear. Three hypotheses suggest themselves: First, the creatinine may be found in the serum in some fashion in the presence of certain muscle disorders. Second, the renal handling of creatinine may be different in the dystrophic patient than in the normal. Third, use of the Jaffé reaction for determination of serum creatinine may have led to falsely high values for serum creatinine in the dystrophic patient as the result of some interfering chromogen in the blood serum.

STUDY OF URINARY COPROPORPHYRIN EXCRETION IN PATIENTS WITH NEOPLASTIC DISEASES. *Howard R. Bierman, M.D., D. Michael Crile, M.D., Louis Strait, Ph.D. and M. K. Hrenoff, B.S. San Francisco, Calif.* (From the National Cancer Institute, National Institutes of Health, U. S. Public Health Service and the University of California Medical School.)

Over many months studies on patients without therapy have shown cyclic increases in coproporphyrin urinary excretion. Patients with various neoplastic diseases treated with nitrogen mustard have shown a pronounced coproporphyrinuria within one to three days after intravenous administration of methyl-bis(beta chloroethyl) amine. While the mechanism of coproporphyrin excretion was exhausted by repeated frequent doses of nitrogen mustard in one case, there appeared to be a stoechiometric relationship in some patients so that increased dosage of nitrogen mustard caused an increased coproporphyrin excretion within the ranges of 0.1 to 0.6 mg. per kg. body weight.

MECHANISM INVOLVED IN THE FAILURE TO RAISE THE WHITE BLOOD COUNT WITH TRANSFUSED LEUKOCYTES. *Austin S. Weisberger, M.D., Robert W. Heinle, M.D. and Richard Hannah, M.D. (by invitation) Cleveland, Ohio.* (From the Department of Medicine, Western Reserve University School of Medicine.)

Failure of blood transfusions to raise the leukocyte count is a common clinical observation. This was studied by transfusing concencentrated suspensions of leukocytes and products of disintegrated leukocytes into rabbits. Leukocyte suspensions were obtained from the peritoneal cavity after distention with physiologic saline. These were concentrated by centrifugation, resuspended in Tyrode's solution and transfused into the veins or arteries of the same (autotransfusion) or other (heterotransfusion) rabbits. Leukocytes were disintegrated with su-

personic vibration, the material centrifuged and the supernatant fluid administered intravenously.

Autotransfusion of leukocytes resulted in sudden, profound leukopenia in fourteen of sixteen rabbits, the average time of onset was 2.8 minutes, average duration 2.2 hours and average decrease in leukocytes 69.3 per cent. Initial leukocytosis never occurred but in nine rabbits subsequent significant leukocytosis developed after an average of 4.3 hours.

Heterotransfusion of leukocytes in seventeen rabbits and administration of cell-free aqueous extracts of disintegrated leukocytes to ten rabbits resulted in a sudden profound leukopenia in every instance similar in all details to the results just described. Subsequent leukocytosis occurred in more than one-half of the animals.

Leukopenia was associated with the appearance of large numbers of cells in the lungs. This was conclusively demonstrated by using leukocytes labeled with radioactive phosphorus. Removal of cells previously circulating and the occurrence of leukopenia after administration of particle-free extracts indicate that this is more than simple filtration of foreign particles. It is evident that leukocytes contain a substance(s) capable of affecting the number of circulating cells. Preliminary experiments indicate that thromboplastin and histamine are not responsible for the effects observed.

Acquired Hemolytic Anemia: Relation of Amount of Erythrocyte Antibody to Activity of the Disease.

Robert S. Evans, M.D. San Francisco, Calif. (From the Department of Medicine, Stanford University School of Medicine.)

An antibody-like agent can be demonstrated on erythrocytes of patients with acquired hemolytic anemia with the Coombs reagent (anti-human globulin rabbit serum), but the observation that abnormal sensitization persists during complete remissions throws doubt on the importance of the antibody as a primary cause of the disease. However, studies in eleven patients with acquired hemolytic anemia indicate a direct correlation between the amount of antibody on the erythrocyte and activity of the disease. The adsorbed antibody is assayed by the susceptibility of the washed erythrocytes to agglutination in serial dilutions of a standard Coombs reagent. It can be shown by analogy with the Rh hyperimmune antibody that the concentration of Coombs reagent necessary to produce agglutination is inversely proportional to the amount of antibody on the cell surface.

The erythrocytes of patients with acquired hemolytic anemia have been agglutinated by dilutions of the Coombs reagent varying from 1 to 2 to 1 to 1,280. The cells of eight patients with active disease before or after splenectomy were agglutinated by high dilutions (1 to 80 to 1 to 1,280) whereas the red cells of seven patients in remission following splenectomy (five) or spontaneous (two) with normal pigment excretion were agglutinated only in dilutions of 1 to 2 to 1 to 80. Two patients studied before and after splenectomy exhibited a sharp reduction in the amount of adsorbed antibody associated with cessation of rapid hemolysis. Spontaneous remission in two patients was observed to follow more gradual reduction of the amount of antibody on the cell surface.

The data suggest that a critical concentration of antibody on the cell is necessary to produce accelerated destruction and that subcritical sensitization is compatible with normal longevity of erythrocytes as measured by normal pigment excretion. Splenectomy, when it is effective, acts by reducing the amount of antibody below the critical level, probably by removal of a certain proportion of the antibody-producing tissue.

Clinical and Metabolic Effects of Different Nutrients in Patients with Cirrhosis.

Gordon R. Morey, M.D. (by invitation), Camen R. Paynter, M.D. (by invitation), C. Frank Consolazio, M.D. (by invitation), Mary A. Maloney, M.D. (by invitation), Louis J. Vorhaus, M.D. (by invitation), Mildred Breimyer (by invitation) and Robert M. Kark, M.D. Chicago, Ill.

Clinical and metabolic observations were made to compare four different types of medical therapy in each of four patients with cirrhosis. The control regimen included a fixed daily intake of calories (twice basal requirement); protein (2.5 Gm./Kg. body weight); fat (30 per cent of total calories); carbohydrate (total calories less calories from protein and fat); salt (0.9 Gm. NaCl) and water (2.5 L.). The 126-day study consisted of seven consecutive eighteen-day metabolic periods. Throughout this time the patients consumed the control diet which was supplemented daily as follows during the

second, fourth and sixth eighteen-day periods: (1) 120 Gm. of salt-poor, 10 per cent amino acid solution, given intravenously; (2) choline, cystine, methionine and B complex vitamins given orally and liver extract given intravenously; (3) salt-poor human serum albumin given intravenously plus the nutrients mentioned in the second category.

The health of all patients improved during the study, as manifested by weight gain without fluid retention, decrease in number and size of vascular spiders, reduction in ascites and edema and in two patients by diminution of the liver size. The only significant change among seven serial liver function tests was in serum cholinesterase activity which correlated closely with clinical variations.

Positive nitrogen balances were observed in all patients throughout the study but were greatest during therapy with intravenous amino acids and with human serum albumin. The urinary excretion of calcium increased during the periods of (1) amino acid therapy and (2) supplementation by lipotropic substances, vitamins and parenteral liver. When sulfaguanidine was given for one day to three patients with diarrhea, a transient sharp rise in urinary calcium excretion was observed, with an increase in one patient up to 1 Gm. per day from a previous value of 0.45 Gm.

PATHOLOGIC AND FUNCTIONAL CHANGES IN THE LIVER FOLLOWING UPPER ABDOMINAL OPERATIONS. *Norman Zamcheck, M.D., Thomas C. Chalmers, M.D. and Charles S. Davidson, M.D. Boston, Mass.* (From the Thorndike Memorial Laboratory, Second and Fourth Medical Services (Harvard), Boston City Hospital, and the Department of Medicine, Harvard Medical School.)

The effects of major surgery on the liver were studied in fifteen patients before and after sixteen operations, including twelve subtotal gastrectomies, three cholecystectomies and one exploratory laparotomy. Serial liver function tests, including bromsulphalein retention (twelve patients), serum bilirubin concentration (six patients) and thymol turbidity and flocculation (six patients) were performed before and after operation. Specimens of the liver were obtained by biopsy from six patients immediately after the abdomen was opened. In fifteen patients, including these six, tissue was obtained at the completion of the operation just before the abdomen was closed.

The tissue obtained at the end of the operation in every patient showed pathologic evidence of acute inflammation of the liver. The lesions were primarily of three types: (1) capsular and subcapsular inflammation; (2) focal collection of neutrophilic polymorphonuclear cells distributed largely around the central vein of the lobule, the portal area being spared in most instances; (3) necrosis of liver cells. In none of the control biopsies obtained at the beginning of the operation were these pathologic changes found. The bromsulphalein retention increased in every instance postoperatively and remained elevated for a variable number of days. Serum bilirubin was increased to above normal in three patients postoperatively. No significant change in thymol turbidity or flocculation occurred.

It is concluded that performance of these major surgical procedures upon the upper abdomen was followed by morphologic and functional evidence of liver impairment. The changes observed appeared to be directly related to the operations rather than to coexistent lesions of the stomach or gallbladder.

STUDIES IN PROTEIN METABOLISM WITH THE AID OF S^{35}-LABELED-METHIONINE. *Laurance W. Kinsell, M.D., Sheldon Margen, M.D., Harold Tarver, M.D., Julie McB. Frantz, M.D., Erin K. Flannagan, M.D., Vernon T. Thompson, U.S.N. and Robert V. Deal, U.S.N. San Francisco, Calif.* (From the Division of Medicine, University of California Medical School, the Metabolic Research Unit, U. S. Naval Hospital-University of California, Division of Biochemistry, University of California, and the Department of Chemistry, Mills College.)

S^{35}-labeled-methionine has been administered to normal males and to patients with (1) chronic liver damage, (2) idiopathic hypoproteinemia and (3) Cushing's syndrome. Incorporation of the labeled material in plasma protein, as well as its excretion in urine and stool, have been quantitated.

From these studies it has been found that incorporation of the S^{35} in plasma protein goes

on more slowly with chronic liver damage than in the normal controls, that its rate of disappearance from plasma protein occurs about at the same rate as in normal individuals and that the S^{35} of urinary sulfate is in accord with these findings. In the patient with idiopathic hypoproteinemia the initial rate of incorporation in plasma protein occurs much more rapidly than in the normal control, after which the rate of disappearance from plasma protein occurs proportionately even more rapidly, with the result that within three weeks this patient is in a net deficit as compared to the control. Again the S^{35} content of urinary sulfate is in agreement with these findings. In the patient with Cushing's syndrome (who was studied only over a three-day period immediately preceding removal of an adrenocortical tumor) the initial rate of incorporation of the S^{35} in plasma protein was significantly more rapid than in the normal control.

From these data one may conclude that S^{35}-labeled-methionine is a valuable tool for quantitation of protein anabolism and catabolism.

A Method of Evaluating Tissue Protein Stores. *John E. Harroun, M.D., Stanley Levey, Ph.D. and Charley J. Smyth, M.D. Eloise, Mich.* (From the Wayne County General Hospital.)

Total circulating proteins and fractions were determined before and thirty minutes after infusion of 1 L. of physiologic saline (at a rate of approximately 20 ml. per minute). Total circulating hemoglobin was determined in several cases. Plasma volumes were measured before and after the infusion using the dye method (T-1824). Sixteen patients, varying in nutritional status from normal to severe malnutrition, were studied. After the initial observations four malnourished subjects were placed upon a high caloric (3,000 to 4,500), high protein (2.5 to 5.0 Gm./Kg./day) diet and studied through the transition from undernutrition to the normal nutritional state. Clinical criteria as to weight gain, subjective symptoms and reversal of abnormal liver function tests were used as guides to the re-establishment of normal nutrition.

The response to the infusion exhibited by patients in normal nutrition was constant and was characterized by an increase in plasma volume of about 400 ml., an increase in total circulating protein of approximately 10 Gm. per square meter body surface and an increase in total circulating hemoglobin in those patients in whom this determination was made. The response exhibited by the malnourished patients also was constant but differed from the normal in that the plasma volume increased about 260 ml., whereas the total circulating protein decreased 10 or more Gm. per square meter of body surface. Total circulating albumin, although not constant in either group, tended to be increased in the presence of normal nutrition and tended to be decreased in undernutrition.

The pattern exhibited by subjects with normal nutrition is interpreted as evidence of adequate labile tissue protein stores. Failure of total circulating proteins to increase after infusion in the malnourished subjects is interpreted as a manifestation of depleted tissue protein stores. That this is the probable mechanism is strengthened by a demonstration of reversal of response from that characterizing malnutrition to that of normal nutrition during the course of a high caloric, high protein diet in four patients so studied.

Serial Biopsy Studies in Cirrhosis of the Liver. *W. D. Davis, Jr., M.D. New Orleans, La.* (From the Ochsner Clinic.)

Studies of the clinical course and response to therapy in twenty-nine patients with cirrhosis of the liver by means of serial liver biopsies as well as the usual laboratory procedures have resulted in reasonable agreement between microscopic and other laboratory findings and the clinical courses of the patients.

In ten patients with clinical manifestations of hepatic decompensation there was microscopic evidence of advanced fibrosis with varying degrees of hepatic cellular necrosis, fatty change, leukocytic infiltration and regeneration of the bile ducts. Of these the only patients who made significant progress under therapy were numbered among the five in whom there were definite fatty changes in the liver. Explanation of this is believed to lie in the fact that hepatic cells, rendered temporarily useless by the presence of large amounts of fat, may regain their function quickly as the fat is mobilized and thus furnish a reservoir of hepatic function which may be utilized by proper therapy. Disappearance of cellular infiltration and edema may contribute in small degree to this effect.

In the compensated group the presence or absence of fatty change seemed to make little difference in the clinical progress which was uniformly good in the patients who followed the therapeutic regimen. These patients frequently improved despite use of low caloric diets with adequate proteins and vitamin supplements. In general they presented less severe degrees of fibrosis, cellular necrosis and regeneration of bile ducts than the decompensated group although there were in many instances leukocytic infiltration and fatty changes.

Diminution in fat could be detected as soon as ten days after the institution of therapy. Cellular infiltration disappeared more slowly whereas in those patients who improved parenchymal hepatic necrosis rapidly disappeared. Diminution in fibrosis was not evident.

Methionine was considered of value particularly in three patients who exhibited rapid diminution in fatty infiltration of the hepatic cells despite a grossly inadequate caloric and protein intake during the period of observation. There was no evidence that methionine was of particular value in those patients who were able to maintain adequate oral alimentation.

EVIDENCE THAT RENAL SODIUM EXCRETION IS CONTROLLED BY ADRENAL CORTICAL ACTIVITY AND INGESTED SODIUM MAY DISPLACE INTRACELLULAR POTASSIUM IN NORMAL SUBJECTS. *Alexander Leaf, M.D. and L. H. Newburgh, M.D.* (*Introduced by Sibley W. Hoobler, M.D.*) *Ann Arbor, Mich.* (From the Department of Internal Medicine, The Medical School, University of Michigan.)

The effects of great variation in sodium intake were studied in normal subjects maintained on fixed diets of adequate calories and protein with very low sodium and chloride content. At definite periods additional sodium was administered either as the chloride or citrate.

Salt restriction resulted in reduction in urinary sodium and chloride to minute amounts accompanied by increase in urinary nitrogen, urea, uric acid, potassium and phosphorus. Administration of sodium chloride or citrate caused high urine sodium with decrease in urine uric acid, potassium, phosphorus, blood and urine urea and positive nitrogen balance. The drop in blood urea was not accounted for by alteration in glomerular filtration rate but was explained by a decrease in the rate of protein catabolism. A strongly positive potassium balance occurred simultaneously with the high sodium excretion that could not be accounted for by decreased protein catabolism.

All these changes are explained by alterations in adrenal cortical activity. The need to conserve body sodium was met by increased activity of the desoxycorticosterone-like hormone. An associated increase in protein-catabolic hormone activity was elicited also. Sodium administration abolished the need to conserve sodium and thus depressed adrenal cortical activity. This not only allowed a large urinary sodium excretion but also gave evidence of a marked decrease in activity of protein-catabolic hormone.

In all subjects sodium citrate administration initially caused a marked positive sodium balance. The degree of alkalosis was reduced by entry of large amounts of sodium into the cells with displacement of large amounts of potassium as evidenced by the strongly negative potassium balance.

CEREBRAL BLOOD FLOW IN VASCULAR DISEASE OF THE BRAIN, WITH OBSERVATIONS ON EFFECTS OF STELLATE GANGLION BLOCK AND NICOTINIC ACID. *Peritz Scheinberg, M.D.* (*Introduced by E. C. Kunkle, M.D.*) *Durham, N. C.* (From the Department of Medicine, Duke University School of Medicine.)

Since the nitrous oxide method for cerebral blood flow, devised by Kety and Schmidt, measures blood flow per unit weight of brain, normal values are obtained regardless of variations in brain size as long as cell function is normal. If the arterial inflow to the normal brain is reduced without affecting cellular function, the arteriovenous O_2 difference widens and O_2 consumption is normal. If cellular metabolism is decreased, arteriovenous O_2 difference is narrowed and O_2 consumption lowered.

This technic, modified by drawing continuous samples of arterial and internal jugular venous blood rather than five separate arterial and venous samples, was used to determine cerebral blood flow in fifteen patients. All patients had hypertensive vascular disease except one who had mitral stenosis with repeated cerebral embolisms. The subjects fell into two groups: (1) those with changes in their mental status

and (2) those without alteration in their mental status but who had papilledema and retinopathy from hypertension.

The patients in the first group showed reductions in cerebral blood flow and only slight increases in arteriovenous O_2 difference, with resulting lowered O_2 consumption. Normal values were obtained in the second group. The decreased cerebral blood flow in the first group probably resulted from increased resistance offered by diseased cerebral vessels. The decreased O_2 consumption cannot be explained by the reduced blood flow alone because other studies show that a chronic reduction in cerebral blood flow can be completely compensated by widened arteriovenous O_2 difference. The decreased O_2 consumption is therefore indicative of cellular dysfunction produced by varying degrees of ischemia.

Unilateral procaine stellate blocks were done on sixteen subjects, including normals and patients with cerebral vascular disease. The blocks caused no significant changes in cerebral blood flow, O_2 utilization or cerebrovascular resistance.

Intravenous nicotinic acid in patients with vascular disease likewise produced no change.

Considerations of Renal, Hepatic and Extremital Arteriovenous Differences in Concentration of Radiomercury of a Mercurial Diuretic.

Pervis Milnor, M.D., George Burch, M.D., Thorpe Ray, M.D., Sam Threefoot, M.D. and Gerald Berenson, M.D. New Orleans, La. (From the Department of Medicine, Tulane University School of Medicine and Charity Hospital of Louisiana.)

Certain aspects of the pharmacodynamics of the mercury in a mercurial diuretic labeled with radiomercury have been studied in seven subjects; in five patients renal venous catheterization was performed and in the other two hepatic venous catheterization. Four subjects were normal, two had chronic congestive heart failure and one had only a right kidney. Samples of arterial blood, extremital and renal or hepatic venous blood, as well as samples of urine obtained by ureteral or vesical catheterization were collected simultaneously.

In general, differences in the arteriorenal venous concentration varied from 5 to 25 per cent, with considerable fluctuation during the initial ten minutes. Thereafter there was a slight but steady decrease in these differences, during which time they were directly proportional to the arterial concentration of the tracer. Differences in concentration between arterial and extremital venous blood were greater than those between either arterial and renal or arterial and hepatic venous blood during the initial five minutes after injection. After ten or twenty minutes no constant differences existed between arterial and extremital venous concentrations. A difference of about 10 per cent in arteriohepatic venous concentration occurred in one normal subject; no constant difference could be detected in the patient with severe chronic congestive heart failure.

The peak of urinary excretion occurred ten to twenty minutes later than the peak of the arteriovenous differences. Urinary excretion varied independently of percentage renal extraction or arterial concentration. Urinary concentration of radiomercury and rate of urinary flow varied discordantly, but each of these functions for two kidneys of the same subjects varied concordantly.

The data indicate a retention of mercury by the kidney, at least during the initial twenty to thirty minutes. An early antidiuretic effect of mercury was noted.

Electrocardiographic Control of Coronary Venous Catheterization in Dogs and Man, and Simultaneous Measurement of Coronary Blood Flow, Cardiac Work and Efficiency.

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Coronary venous catheterization has proven feasible under fluoroscopic visualization in eight of eleven recent attempts in man and in 98 per cent of one hundred dogs. Alternate posteroanterior and right anterior oblique views provided the stereoscopic effect necessary to identify pertinent landmarks associated with the coronary sinus and cardiac veins. With a specially

designed catheter, blood was easily withdrawn from coronary veins without evidence of significantly obstructing coronary venous return. Withdrawal of very dark desaturated blood and observance of mean pressures only 2.3 mm. higher than right auricular pressure with a characteristic pressure pattern helped to confirm successful insertion. Final confirmation and more precise localization of the catheter tip was obtained from the electrocardiographic complexes obtained from a catheter tip lead, compared with a simultaneous limb lead. Complexes were obtained in the great cardiac vein, coronary sinus, posterior left ventricular vein and middle cardiac vein which were characteristic of each location, and were readily distinguishable from tracings with the tip in the right auricle or ventricle.

Adaptation of the cerebral flow method of Kety and Schmidt has permitted calculation of coronary blood flow simultaneously with coronary arteriovenous oxygen difference and cardiac work measured from the product of cardiac output and systemic blood pressure. Left ventricular efficiency in man, calculated from these observations in five normal patients, was 17 per cent (0 = ±7%). Duplicate or triplicate normal coronary blood flows showed a maximum spread of 18 per cent and a mean value of 87 cc./100 Gm. of left ventricle/min. Myocardial oxygen consumption was 11 to 21 cc./100/Gm./min., relatively constant in each subject.

Coronary venous catheterization appeared innocuous and less hazardous than catheterization of the right ventricle or pulmonary artery.

RELATIONSHIP OF QUINIDINE BLOOD LEVELS TO THERAPY OF CARDIAC ARRHYTHMIAS. *Maurice Sokolow, M.D. and Archie L. Edgar, M.D. San Francisco, Calif.* (From the Medical School, University of California.)

The quantitative aspects of quinidine therapy were investigated by determining multiple blood and urine concentrations (using the photofluorometric extraction method of Brodie, as modified by Lilienthal) during conversion of auricular fibrillation and flutter to sinus rhythm. The inverse relationship between rising blood levels and falling auricular rates found during therapy indicated the relationship between blood quinidine levels and the cardiac effects of the drug. Sinus rhythm was re-established in twenty-four of twenty-eight therapeutic attempts (85 per cent conversion). The average peak blood level at the time of conversion was 6.3 mg./L. Seventy-five per cent of the patients were converted with levels between 4 and 8 mg./L. In only three patients was the level required for conversion less than 4 mg./L. The amount of quinidine required for conversion (resulting in peak levels greater than 4 mg./L.) was usually 0.4 or 0.6 Gm. given every two hours for five doses. In the four patients who failed to convert levels of between 7 and 13.7 mg./L. were obtained. The maximum concentration following a given dose of quinidine was reached in two to three hours and by four hours the blood level had begun to fall. The increment in blood level obtained by successive identical doses became progressively smaller so after four or five doses to increase further the blood level larger individual doses were required. The rapidity of the rise of blood quinidine was much greater when a two-hour schedule was used as compared to a four-hour schedule.

There were eight relapses with four reconversions. Reconversion in the other four was not attempted. Maintenance dose schedules ranged from 0.2 Gm. three times a day to 0.4 Gm. six times a day. Inadequate mid-day peaks were obtained with less than 0.4 Gm. three times a day; therefore, adequate maintenance doses of quinidine should probably be at least 0.4 Gm. four times a day.

The data presented emphasize a more rational method of quinidine therapy for both conversion of arrhythmias and for maintenance of sinus rhythm.

EFFECT OF ABDOMINAL COMPRESSION ON CHLORIDE EXCRETION FOLLOWING ADMINISTRATION OF HYPERTONIC SALINE SOLUTION. *W. H. Cargill, M.D., W. B. Fackler, M.D., R. L. McWhorter, Jr., M.D. and J. V. Warren, M.D. Atlanta, Ga.* (From the Departments of Physiology and Medicine, Emory University School of Medicine and the Medical Service, Lawson VA Hospital.)

It is generally agreed that edema formation in congestive heart failure is associated with a reduction of renal blood flow and glomerular filtration rate. Whether salt retention is due to these changes alone or to extrarenal factors has been the subject of much controversy. The present studies have been undertaken in an

attempt to elucidate further the mechanisms of the altered salt excretion in congestive failure.

The renal blood flow, glomerular filtration rate and chloride excretion have been studied before and after rapid intravenous administration of 250 cc. of 4 per cent saline solution in a group of ten subjects. In addition to studies in the basal state observations were made during a period of increased abdominal pressure produced by an abdominal binder inflated to a pressure of 80 to 100 mm. Hg. In normal subjects without abdominal compression the saline solution produced an immediate increase in the chloride excretion. With the abdominal binder inflated, however, there was no increase in chloride excretion following the saline injection. The saline injection in itself did not significantly alter the renal blood flow or glomerular filtration rate, but abdominal compression usually resulted in a considerable diminution in blood flow and filtration rate. Increased abdominal pressure alone produced a fall in the basal rate of chloride excretion. Results similar to those in normal subjects were obtained in a patient with diabetes insipidus indicating that activity of the posterior lobe of the pituitary gland was not responsible for these changes.

These experiments demonstrate that increased intra-abdominal pressure results in a failure normally to excrete injected sodium chloride solution. The situation so produced is in many ways similar to that seen in congestive heart failure.

USE OF OXYGEN CONSUMPTION DURING EXERCISE AS A QUANTITATIVE MEASURE OF CARDIAC RESERVE. *Kenneth Chesky, M.D. and Herbert S. Sise, M.D. Boston, Mass.* (From the First and Third Medical Services, Boston City Hospital and the Department of Medicine, Tufts Medical School.)

The purpose of this study was to devise a simple test as a quantitative measure of cardiac function based on oxygen consumption during exercise. It was found that normal subjects increase the oxygen consumption in linear fashion with increasing increments of exercise while cardiac patients showed either (1) a low fixed or "maximal" oxygen consumption during increasing increments of exercise, (2) oxygen consumptions which were subnormal for work loads of moderate intensity but which were not fixed, (3) oxygen consumptions which resembled normal individuals.

The patients were exercised on a bicycle ergometer at three speeds with a standard brake tension. Oxygen consumptions were determined with a standard Benedict-Roth basal metabolism machine. The slope of the tracing was checked by two maximal inspiratory efforts before and after the second minute of exercise. Normals for these grades of exercise consisted of 346 $\pm$ 57, 564 $\pm$ 77 and 690 $\pm$ 81 cc of oxygen per square meter of body surface. It was found that the clinical degree of incapacity of thirty-two patients corresponded well with the degree of limitation of oxygen consumed during either the greatest of the three exercises or the greatest exercise that the patient could tolerate. Most ambulatory cardiacs, with the exception of patients with severe mitral stenosis, could tolerate all three degrees of exercise. In three patients with myocardial disease the oxygen consumption for a given grade of exercise was increased from 360 to 467, 387 to 517 and 477 to 622 cc./minutes/square meter of body surface thirty minutes after administration of 1.6 mg. of cedilanid intravenously. One case of unsuspected failure was picked up by this test and the response to digitalis. In two patients with mitral stenosis the oxygen consumption with the given degrees of exercise fell from 595 to 546 in one, and insignificantly in another from 700 to 690 cc./minutes/square meter of body surface thirty minutes after cedilanid. Withdrawal of digitalis has been associated with a fall in maximum oxygen consumption of 467 to 315 cc./minutes/square meter of body surface in a patient with hypertensive disease. There was no change in a patient with valvular disease upon withdrawal of digitalis.

In the experience of the authors this is a valuable and simple clinical test of cardiac function.

HEMODYNAMIC EFFECTS OF HYPOTENSIVE AGENTS IN MAN. *Edward D. Fries, M.D., Joseph R. Stanton, M.D., Julius Litter, M.D., James W. Culbertson, M.D., Meyer H. Halperin, M.D., F. Corbin Moister, M.D. and Robert W. Wilkins, M.D. Boston, Mass.*

In order to clarify the mode of action of drugs used in the treatment of essential hypertension the hemodynamic effects of four drugs, each

representative of a class of hypotensive agents, were studied: sodium nitrite (direct-acting peripheral vasodilator), dihydroergocornine (sympatholytic agent), sodium amytal (sedative) and veratrum viride (reflex, neurogenic vasodilator). These were compared as to their effects on cardiac output (Fick), mean arterial pressure, total peripheral resistance, muscle and hepatic-portal blood flows, renal clearances and sympathetic vasopressor reflexes in man.

Drugs which influence central nervous system vascular centers (veratrum, dihydroergocornine) lowered total peripheral resistance without reduction in cardiac output or compensatory tachycardia. Peripheral vasodilators (sodium nitrite) lowered both cardiac output and pulmonary arterial pressure with compensatory tachycardia. The response to amytal was variable and in subhypnotic doses the drug was seldom hypotensive. Following all drugs the muscles usually exhibited greater vasodilatation than the hepatic-portal area while the renal vasculature manifested an autonomy of tone characterized by an initial reduction in BF and GFR followed by a quick return to control values regardless of continuing hypotension. Dihydroergocornine and other sympatholytic agents inhibited vasoconstrictor reflexes but exhibited variable hypotensive responses whereas veratrum, which also acts through the nervous system, did not inhibit sympathetic vasoconstrictor nerves but produced hypotension more uniformly.

These results suggest that following hypotensive drugs (1) the autonomy of the kidney vasculature prevents prolonged alteration of renal hemodynamics, (2) vasodilatation occurs with greater frequency in muscles than in the hepatic-portal area. Following drugs which act through central nervous system vascular centers an integrated hypotensive response occurs. In addition the studies with veratrum suggest that nerves other than sympathetic vasoconstrictors should be considered in regard to the neurogenic regulation of arterial pressure.

RELATIONSHIP BETWEEN SERUM ANTIDIURETIC SUBSTANCES AND URINARY CORTICOSTEROID IN THE HUMAN. *Charles W. Lloyd, M.D. and Julia Lobotsky, M.S. Syracuse, N. Y.* (From the Syracuse University College of Medicine.)

A relationship between adrenal cortical steroids and the posterior pituitary antidiuretic hormone has been postulated (Silvette and Britten). Birnie, Eversole and Gaunt have recently devised a method for measuring in rat serum antidiuretic substances which may be of posterior pituitary origin. In our laboratory the method of Daughaday, Jaffe and Williams for estimation of freely water-soluble adrenal cortical steroids has been modified to permit measurement of poorly water-soluble steroids. A study of the relationship in the human between serum antidiuretic activity, urinary corticosteroid, volume and chloride has been made.

Blood for assay of antidiuretic activity was drawn at the completion of a twenty-four-hour urine collection period. Measurements of the twenty-four-hour corticosteroid and chloride excretion were made. A relative increase of the antidiuretic substance in the ratio

$$\frac{\text{serum antidiuretic substance}}{\text{urinary corticosteroid}}$$

is associated with water retention and a relative increase of the urinary corticosteroid is associated with diuresis. During the crisis in Addison's disease a preponderance of antidiuretic activity with low corticosteroid excretion is found. The increase in corticosteroid excretion following treatment with desoxycorticosterone is associated with a decrease in serum antidiuretic substance. In diabetes insipidus a relatively or absolutely low value of antidiuretic material is present. The cirrhotic who retains water has a preponderance of antidiuretic activity; when diuresis occurs, the corticosteroid level may be very high and the serum may contain no antidiuretic material. In premenstrual water retention a preponderance of antidiuretic activity is found.

ADRENOCORTICAL HYPERACTIVITY IN ACROMEGALY WITH SEVERE DIABETES: HORMONAL AND CLINICAL REMISSION AFTER TREATMENT. *William H. Daughaday, M.D. and Cyril M. MacBryde, M.D. St. Louis, Mo.* (From the Department of Internal Medicine of Washington University Medical School.)

Clinical, biochemical and hormonal studies have been made on a male patient, aged thirty-eight, with acromegaly associated with severe diabetes and insulin resistance. When first observed, only impaired glucose tolerance with-

out clinical diabetes was present. Severe diabetes appeared six months later with great suddenness. Control of the diabetes required a daily dose of insulin from 250 to 500 units over a period of about one year. He was treated with irradiation to the pituitary, stilbestrol and later methyl testosterone. While receiving methyl testosterone a remission occurred so that glycosuria became minimal even without insulin treatment.

We have attempted to elucidate the mechanism of insulin resistance in this patient by biochemical and hormonal studies. During the phase of severe diabetes there was severe lipemia and hypercholesterolemia. Upon subsidence of the diabetes the blood fats and cholesterol almost returned to normal. An attempt was made to demonstrate a factor in the patient's serum inhibiting peripheral utilization of glucose. However, the patient's serum did not inhibit the uptake of glucose by the isolated rat diaphragm.

During the active period of diabetes there was an elevation in the excretion of urinary "cortin" as measured by the liberation of formaldehyde from steroid residues. Values obtained were 1.9, 3.5, 2.4, 4.8 mg. per day (normal, circa 0.75 to 2.0 mg.). Excretion of 17-ketosteroids was a high normal with values from 16 to 36 mg. per day. Following clinical remission cortin excretion fell to 0.81, 0.85, 1.1 mg. per day and the 17-ketosteroids were also reduced to 4.5, 4.7 and 5.4 mg. per day.

The insulin resistance here described is probably hormonal in type and can be partly explained by adrenal cortical hyperfunction. An additional direct pituitary diabetogenic factor was not demonstrated but is presumed also to have been active.

Experimental Evidence on the Mechanism of Diabetic Ketosis.

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(From the New York Hospital and the Departments of Medicine and Psychiatry of Cornell University Medical College.)

In a study of twenty-five human subjects with diabetes mellitus approximately fifty instances of clinical ketosis were observed to occur in a setting of emotional conflict and in the absence of other pertinent factors including infection. Moreover, day to day observation of these subjects both in and out of the hospital yielded a close correlation between life situations, emotion and the metabolic state as reflected by glycosuria, ketonuria, insulin requirement and the symptoms of diabetes.

In an experimental study of nine of the subjects quantitative measurements of blood ketone and glucose concentrations and concomitant determination of urine volume and glucose were made before, during and after an interview in which intense emotional conflict was engendered. Ages of the patients varied from fourteen to sixty years and insulin requirements from 0 to 100 units per day. The chemical determinations were made on either peripheral venous blood or on blood withdrawn directly from a catheter introduced into the hepatic vein. In all cases a significant elevation of blood ketones, as well as a marked increase in the urine volume and rate of urinary glucose excretion, occurred during the traumatic interview. In the most severe diabetics the rapidity and degree of the increase in blood ketones and urine sugar was greatest, but nevertheless a marked degree of ketosis was produced in one of the mildest diabetics when the traumatic conflict situation was prolonged. The level of the blood glucose also fluctuated significantly and was usually lower at the end than at the beginning of the experimental period.

Thus significant emotional conflict has been shown to be associated with a rise in the blood ketone level and a simultaneous "washing out" of glucose through diuresis. The evidence indicates that such a mechanism is commonly involved in the decompensation of diabetes and the production of clinical ketosis.

Effect of Administration of Potassium Based on Study of the Human Subject and the Dog.

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(From the Divisions of Cardiology and Chemistry, Philadelphia General Hospital and the Robinette Foundation, University of Pennsylvania.)

Potassium is frequently administered to patients who have varying degrees of hypopotassemia. The problem of determining the maximum therapeutic and early toxic action is of considerable importance. Its chemical estimation, while highly desirable, is not always available initially or during the various phases

of its administration. This problem was studied during the intravenous injection of 200 to 1,500 cc. of an isotonic solution of potassium chloride over a period of one to six hours in sixty human subjects, the ages of whom ranged from twenty to eighty years, for the following indications: During the hypopotassemic phase following treatment of diabetic acidosis, following fluid loss due to intestinal obstruction and other causes, inanition, diarrhea and other conditions. During administration of potassium these patients were studied clinically, by continuous electrocardiographic tracings and frequent estimation of the serum levels of this electrolyte. The results of these studies have indicated that the electrocardiogram is valuable in following potassium effects and gives early evidence of its toxic action. The range of safety is apparently considerable. Since potassium produces its toxic effect chiefly on the heart and because this electrolyte is administered to patients with varying degrees of myocardial damage which could conceivably alter the toxic dose, a study was performed on normal dogs and dogs with myocardial infarction. The evidence of the initial and varying stages of its toxic effects were noted in the electrocardiogram and correlated with the level of the serum potassium. It was found that the tolerance of dogs with mild degrees of myocardial infarction did not vary much from the normal. In dogs with moderate to severe grades of myocardial infarction there was a definite diminution in tolerance to potassium. The determination of the initial toxic effect by serial electrocardiograms taken during administration of potassium is of help in determining the dose to be given since the cardiac changes in this stage are reversible.

Significance of Electrolyte Abnormalities in Management of Anuria, Oliguria and Edema.

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Anuria, oliguria and edema are associated with significant abnormalities in the electrolyte concentrations of both plasma and urine. When similar changes are produced experimentally in man and animals, marked impairment of renal function follows.

Observations were made in ten patients with anuria or oliguria resulting in rapid elevation of their blood urea nitrogen. Three patients had also developed edema and ascites. In all instances plasma sodium and bicarbonate were reduced and chlorides relatively elevated. In the urine the concentration of sodium was low and the chlorides exceeded the sodium; potassium was variable.

Hypertonic (1 molar) sodium lactate or acetate was administered orally to six patients in sufficient amounts to adjust their plasma electrolytes toward normal. Plasma volume expanded as gauged by hematocrit measurements (presumably as water was withdrawn from cells previously subjected to the hypotonic extracellular fluid); repeated doses of sodium salts were required before the plasma sodium and bicarbonate reached normal. The urinary output increased gradually and diuresis with reduction in blood urea nitrogen occurred in these patients after the plasma sodium and bicarbonate had approached normal. Repeated measurements of distribution of radioactive sodium and changes in both body weight and edema were correlated with readjustment of the plasma to isotonicity and excretion of more water than sodium.

The data indicate clearly that attainment of normal tonicity and volume of the plasma are of primary importance for restoration of renal function.

Evaluation of Pancreatic Function by Means of Induced Hyper-amylasemia following Morphine and Secretin.

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An attempt was made to evaluate pancreatic function by means of an injection of morphine and secretin in forty-four subjects, including twenty-five control patients, eight patients with cancer of the pancreas, six with pancreatitis and five with cancer of the stomach. A fasting blood sample was taken to determine the basal serum amylase; 10 to 15 mg. of morphine sulfate was given subcutaneously and 1 unit of secretin per Kg. was injected intravenously thirty minutes later. Blood samples were taken at fifteen,

thirty, sixty and ninety minutes thereafter for serum amylase determination.

In the twenty-five control patients the average basal value was 133.5 units; following an injection of secretin the peak value occurred at the end of the thirty or sixty-minute interval, with an average value of 389.3 units. In the patients with cancer of the pancreas pre- and post-stimulation and peak values were significantly lower than in the control patients. In 62.5 per cent of these patients amylase values were below the lowest obtained in the control patients before stimulation and after stimulation 50 to 75 per cent had values lower than the minimal control figure. In the other two pathologic groups there was little difference from the control subjects. In three of the six patients with pancreatitis, pain identical with the clinical attack was produced following injection of secretin.

Animal experimentation has shown that injection of secretin after obstruction of the pancreatic ducts results in a transitory rise of the serum enzymes of pancreatic origin. This phenomenon depends on the presence of actively secreting acinar tissue because elevation of the blood enzymes does not occur after the gland atrophies. We achieved obstruction of the pancreatic duct by means of morphine and stimulation of acinar activity by secretin. On the basis of the lower values obtained in patients with cancer of the pancreas we may assume there is a decrease in functioning acinar tissue and therefore believe this procedure may have diagnostic value.

Action of Acetyl-beta-methylcholine Chloride (Mecholyl) on the Human Colon.

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In a physiologic study of patients with functional bowel disease two types of alteration in motility of the sigmoid were noted. Motility is increased in individuals with constipation and diminished in individuals with diarrhea. To elucidate the mechanism of these motility patterns we examined the effects of certain drugs influencing the autonomic nervous system. Mecholyl (acetyl-beta-methylcholine chloride), an agent which is known to produce diarrhea, was found by White and Jones to reproduce many of the symptoms and proctoscopic signs of mucous colitis. We studied this drug intensively by means of kymographic recordings of pressure changes in an in-lying sigmoid balloon or by continuous proctoscopic observations of the rectosigmoid.

Mecholyl has been administered subcutaneously in amounts ranging from 2.5 to 10.0 mg. to twenty subjects. In fifteen of forty experiments marked diminution of wave-like motility in the sigmoid colon accompanied the usually observed effects of this drug. When these effects disappeared, the previous pattern of motility was resumed. In no instance did mecholyl produce augmentation of motility. When the rectosigmoid was observed proctoscopically in four normal subjects, mecholyl produced no significant changes in color or contractility. The aforementioned effects of mecholyl were blocked by atropine. In a patient with a transverse colostomy motility tracings were obtained from the cecum, splenic flexure and sigmoid. Mecholyl caused a marked increase of cecal activity, moderate stimulation of the transverse colon and cessation of motility of the sigmoid.

Thus mecholyl appears to stimulate the right colon and inhibit wave-like activity of the sigmoid, effects which enhance the evacuation of intestinal contents. It is inferred that the mechanism of emptying the bowel may be entirely a cholinergic phenomenon. It is of interest that most patients with functional diarrhea or ulcerative colitis spontaneously exhibit a similar diminution of wave-like motility of the sigmoid.

Use of Maxted's Enzyme Method for Grouping Beta-hemolytic Streptococci.

Lewis W. Wannamaker, M.D., Floyd Denny, M.D., William R. Brink, M.D. and Edward Custer, M.D. (*Introduced by C. H. Rammelkamp, M.D.*) (From the Streptococcal Disease Laboratory, Fort Francis E. Warren, Wyoming and the Department of Preventive Medicine, Western Reserve University, Cleveland, Ohio.)

During the course of a field study of streptococcal diseases at Ft. Francis E. Warren, Wyo., 692 strains of beta-hemolytic streptococci were isolated, of which 551 strains were grown from the throats of hospitalized respiratory patients and the remaining 141 strains were obtained

from routine cultures of normal soldiers. All 692 strains were successfully lysed by Maxted's enzyme which is produced by a strain of Streptomyces albus. A loopful of growth from a blood agar plate was inoculated into 0.25 cc. of the enzyme preparation and the mixture was placed in a water bath at 50°C. for two to twenty-four hours. After complete clearing had occurred the lysate was used as an antigen for grouping with rabbit antisera. Using the capillary tube technic, all 692 strains gave definite precipitin reactions with one of the more common groups. 672 strains (97 per cent) were found to be group A, two were group B, eleven were group C and seven were group G. Formamide extracts prepared by the method of Fuller were set up in parallel on the first 341 strains. In no case was there disagreement in the two methods. Groupings were checked on an additional seventy-nine strains by preparing hot acid extracts which were set up against group specific antisera. These results were also in complete agreement with those obtained by the enzyme method. It is suggested that Maxted's enzyme offers an efficient, rapid method for identifying group A beta-hemolytic streptococci.

PRIMARY SUTURE OF THE DIVIDED TRACHEA. *Bernard Maisel, M.D. and James A. Dingwall, M.D. New York, N. Y.* (From the Department of Surgery, New York Hospital and Cornell University Medical College.)

Primary anastomosis of the cervical trachea following a cut throat injury was successfully carried out by one of us approximately two years ago. This was done without tracheotomy or drainage of the adjacent soft tissues. Stimulated by this an experimental study was undertaken in order to determine the physiologic processes of healing attendant on surgical repair of the trachea as representative of a cartilaginous organ.

In this preliminary study a small series of dogs was used. In one group, after exposure of the trachea through a midline neck incision, the trachea was completely divided and then immediately sutured employing continuous everting mattress sutures. Leaks were tested by submerging the joined segments in saline. In a second series complete segments measuring up to 2½ cm. in length were removed and the continuity of the trachea was re-established as described. These animals were then observed by endoscopic examination, and specimens were removed at intervals of from one to six weeks for microscopic study. In all instances healing occurred or successful, leak-proof union was maintained by what is recognized surgically as primary union. No leaks occurred giving rise to subcutaneous crepitus or infection, and adequate airways were maintained without any appreciable stricture formation.

Although few, there are reports in the literature suggesting the feasibility of direct tracheal anastomosis. Recently Daniel gathered excellent evidence to show the remarkable autoregenerative ability of tracheal tissue about temporary prostheses, and Longmire reported the repair of an old post-traumatic defect by the temporary use of a lucite tube to bridge a gap in the cervical trachea. We believe that primary anastomosis of the trachea and bronchi may be entirely feasible in humans not only in repairing traumatic injuries but in resections of pulmonary and esophageal lesions where invasion of the air tube would seem to limit operability.

EFFECT OF AUREOMYCIN ON THE SURVIVAL OF VIRUS IN LYMPHOGRANULOMATOUS BUBOES. *John W. Runyan, M.D., Lisbeth M. Kraft, M.D. (by invitation) and Irving Gordon, M.D. Albany, N. Y.* (From the Department of Medicine, Albany Medical College, and the Division of Laboratories and Research, New York State Department of Health.)

Viruses of the lymphogranuloma venereum-psittacosis group frequently induce a carrier state. Since aureomycin has proved effective in the treatment of both clinical and experimental lymphogranuloma venereum, we wished to learn whether the virus persists in buboes during clinical improvement. Two patients were studied. Oral treatment with 24.5 and 19.5 Gm. of aureomycin for nine and ten days, respectively, resulted in high serum aureomycin levels and definite regression in the size of the buboes by the fourth day. Three weeks after treatment commenced the buboes had disappeared.

To detect the virus, bubo aspirates were inoculated intracerebrally in mice and into the yolk sacs of embryonated hens' eggs. The virus was isolated from each patient in the first five consecutive attempts: three times prior to

therapy and on the first and second days of treatment. Attempts at isolation were unsuccessful on the fourth and seventh days of treatment.

While the data do not permit decision as to whether subinfective quantities of virus still survived in the healed lymph nodes, the results indicate that infectivity does not persist for long following treatment. This is consonant with the rapid disappearance of the buboes.

CLINICAL EXPERIENCE WITH THE 4-AMINO DERIVATIVES OF PTEROYLGLUTAMIC ACID AND 2,6-DIAMINOPURINE IN THE TREATMENT OF NEOPLASTIC DISEASE. *J. H. Burchenal, M.D., D. A. Karnofsky, M.D., C. M. Southam, M.D., W. P. L. Myers, M.D., L. F. Carver, M.D., H. W. Dargeon, Jr., M.D., C. P. Rhoads, M.D. New York, N. Y.* (From the Sloan-Kettering Institute and Memorial Hospital.)

A total of eighty-two patients have been treated with various derivatives of pteroylglutamic acid characterized by the substitution of an amino group in the 4 position of the pteridine ring. Among these patients were thirty-four acute leukemias, fifteen chronic leukemias, ten lymphosarcomas, seven Hodgkins' disease, three osteogenic sarcomas, two Ewing's tumors, two neuroblastomas, two mycosis fungoides, two carcinomas of the lung and one each of the stomach and bladder, one fibrosarcoma, one multiple myeloma and one eosinophilic granuloma.

With the 4-amino derivatives of pteroylglutamic acid, toxic symptoms of stomatitis, diarrhea, gastrointestinal bleeding and loss of hair were occasionally seen. With 2,6-diaminopurine the most troublesome toxic symptoms were severe nausea and vomiting which often made adequate dosage impossible. Both types of drugs when pushed to toxic levels caused leukopenia and definite depression of the bone marrow.

Complete although temporary clinical remission in acute leukemia with reversion of the bone marrow to approximately normal was seen in four of twenty children, and one of fourteen adults treated with the 4-amino derivatives of pteroylglutamic acid. A second remission has thus far been induced by further therapy in all patients who relapsed following the first remission. In lymphosarcoma and eosinophilic granuloma in children and chronic myelocytic leukemia in adults temporary clinical remissions occurred occasionally after therapy with the 4-amino derivatives. In lymphomas and other forms of neoplastic disease in adults no useful therapeutic results were noted.

EXPERIMENTAL EVIDENCE ON RELATIVE EFFECTS OF LIFE STRESS AND INHALED POLLEN IN HAY FEVER. *Thomas H. Holmes, M.D., Theodore F. Treuting, M.D. and Harold G. Wolff, M.D. New York, N. Y.* (From the New York Hospital and the Departments of Medicine and Psychiatry, Cornell University Medical College.)

An experimental attempt was made to clarify the relative importance of distressing life situations and inhaled pollens in the pathogenesis of hay fever. In thirty subjects, fifteen of whom had had hay fever, repeated quantitative studies of nasal function were made under uniform conditions in a room in which a known concentration of pollen was circulated. Nasal hyperfunction characterized by varying degrees of hyperemia, swelling and hypersecretion of the membranes as well as eosinophilia in the nasal secretions and circulating blood occurred in all subjects, "sensitive" or "normal," exposed to mixed ragweed pollen when the circumstances were appropriate.

When nasal function was average, neither sensitive nor normal subjects reacted to mixed ragweed pollen with sufficient evidence of nasal hyperfunction to produce symptoms. However, when there was pre-existing nasal hyperfunction from whatever cause, both groups reacted to the pollen with marked hyperfunction, weeping and sneezing. Thus during difficult life situations productive of conflict typical hay fever attacks followed pollen inhalation. Conversely, it was possible during pollen inhalation in the absence of frank hay fever to induce an attack by a discussion of significant personal problems and to induce subsidence of the attack by reassurance while the pollen is still being inhaled.

Unilateral procaine block of the stellate ganglion in ten subjects yielded evidence that nasal hyperfunction engendered by conflict situations was mediated through parasympathetic fibers in the greater superficial petrosal nerve. Inhalation of pollen following this procedure precipitated the signs and symptoms of unilateral rhinitis which spared the non-hyperfunctioning membrane on the uninjected

side. It was concluded that sensitive individuals differ from normals only in degree, that pollen or distressing life situations may induce nasal hyperfunction in either with associated local and circulating eosinophilia and symptoms of rhinitis. The various factors provocative of nasal hyperfunction with symptoms of hay fever thus exert an additive effect.

ERYTHROPOIETIC ACTIVITY OF EXTRINSIC FACTOR ON PARENTERAL ADMINISTRATION IN PERNICIOUS ANEMIA. *Frank H. Gardner, M.D., John W. Harris, M.D. and William B. Castle, M.D. Boston, Mass.*

According to Castle, interaction between the food (extrinsic) factor and the gastric (intrinsic) factor is required for the formation of the anti-pernicious anemia principle of liver—here considered to be vitamin B_{12}. The complete reaction does not occur *in vitro*. We have shown recently that the erythropoietic effect of orally administered vitamin B_{12} is enhanced by the simultaneous administration of the gastric (intrinsic) factor although not to the extent observed when the same amount of vitamin B_{12} is given alone parenterally.

In the present observations a daily dose derived from 400 Gm. of beef muscle was employed in the form of an autoclaved, 70 per cent alcohol filtrate of an aqueous extract of beef muscle from which the alcohol had been removed by free evaporation. In three patients with untreated pernicious anemia the preparation was inert upon daily oral administration, was moderately active when orally administered daily together with 150 cc. of normal human gastric juice and still more active upon intravenous administration without gastric juice. Microbiologic assays and erythropoietic effects indicate the presence of somewhat less than 1 microgram of vitamin B_{12} in each daily dose of the beef muscle extract.

Comparisons of blood glucose and tyrosine levels following oral administration of these substances simultaneously with 150 cc. of normal human gastric juice or an equal amount of salt solution upon alternate days indicate no non-specific effect upon absorption attributable to the gastric (intrinsic) factor. This suggests the possibility that the food (extrinsic) factor is identical with or chemically closely related to vitamin B_{12} and that the gastric (intrinsic) factor is essential merely for facilitation of absorption of low concentrations of vitamin B_{12} present in certain foods other than, for example, liver.

RELATIONSHIP BETWEEN ELECTROCARDIOGRAPHIC EVIDENCE OF RIGHT VENTRICULAR HYPERTROPHY AND PULMONARY ARTERIAL PRESSURE IN CHRONIC PULMONARY DISEASE. *John B. Johnson, M.D. (by invitation), John R. West, M.D., M. Iréné Ferrer, M.D., H. M. Weiner, M.D. and André Cournand, M.D. New York, N. Y.* (From the Bellevue Hospital.)

This paper presents a group of thirty-eight patients with chronic pulmonary disease in whom studies of the pulmonary arterial pressure at rest and electrocardiographic evidence of right ventricular hypertrophy were made. The purpose of the study was to determine whether any correlation exists between pulmonary arterial pressures and electrocardiographic signs of right ventricular hypertrophy. The patients were studied by the right heart catheterization technic. The electrocardiographic study included measurements of the R/S ratio and the intrinsicoid deflections in the unipolar precordial V leads.

The patients were divided into three groups. Group I included nine patients with normal pulmonary arterial mean pressures at rest (15 mm. Hg or less) but whose mean pressures were elevated with exercise. Group II included sixteen patients with elevated pulmonary arterial mean pressures ranging from 16 to 30 mm. Hg. Group III included twelve patients with resting pulmonary arterial mean pressures above 30 mm. Hg. The electrocardiograms in group I showed no evidence of right ventricular hypertrophy. Group II, which included those with marked chronic pulmonary emphysema, fibrosis or both, also showed no specific electrocardiographic evidence of right ventricular hypertrophy although one patient showed an incomplete right bundle branch block. Nine of the twelve patients in group III showed specific electrocardiographic signs of right ventricular hypertrophy of incomplete right bundle branch block. One patient showed presumptive evidence of right ventricular hypertrophy. A high incidence of incomplete right bundle branch block (14 per cent) was found in thirty-seven patients.

The data suggest that most patients with chronic pulmonary disease whose resting pul-

monary arterial mean pressures exceed 30 mm. Hg will have right ventricular hypertrophy as indicated by the unipolar precordial V leads of the electrocardiograms. With lesser degrees of pulmonary arterial hypertension in this small series of patients, the electrocardiograms were of no value in the detection of right ventricular hypertrophy.

EFFECT OF LYSOZYME ON GASTRIC AND COLONIC MUCUS OF MAN *in Vitro*. *George B. Jerzy Glass, M.D. and Betty L. Pugh, M.D.* (*Introduced by Stewart Wolf, M.D.*) *New York, N. Y.* (From the Departments of Medicine and Psychiatry of the New York Hospital and of the Cornell University Medical College.)

Meyer and others have demonstrated that in human subjects with peptic ulcer and ulcerative colitis a significant increase occurs in the concentration of the mucolytic enzyme lysozyme in the gastric juice and stools, respectively. In view of the possibility that lysozyme acts to destroy the natural mucus coating of the stomach and bowel it seemed pertinent to explore *in vitro* the effect of lysozyme on human gastric and colonic mucus.

Tests for lysozyme activity were carried out by the viscosimetric method of Meyer, by volumetric measurement and by chemical analysis of products of mucus digestion. Purified egg white lysozyme and human tears containing approximately 500 units of lysozyme per cc. were used. The gastric mucus was obtained from normal subjects, achlorhydric subjects and from a fistulous human subject with a completely occluded esophagus. His gastric juice was thus free from contamination from saliva and nasorespiratory mucus. The colonic mucus was obtained directly from three fistulous human subjects with exposed evaginated segments of bowel.

Both the gastric and colonic mucus were tested in their native state at various pH values and after liquefaction by incubation or solution in dilute alkali. The mucus was also fractionated by the method of Glass and Boyd into its components, dissolved mucoprotein elaborated by the mucus cells of the gastric glands and visible mucus and mucoproteose derived from the lining columnar epithelial cells. No mucolytic action was displayed *in vitro* by lysozyme on human gastric or colonic mucus. Neither whole mucus in its various preparations at various pH values nor any of the fractions of mucus from the stomach or colon were measurably changed by egg white or human lysozyme in tears. In the stomach another mucolytic enzyme was detected which was neither lysozyme nor pepsin. Contact of lysozyme with gastric mucus neither impaired nor enhanced the activity of the lysozyme on its mucinous bacterial substrate.

These observations lead to the inference that whatever the consequences of increased lysozyme secretion in ulcerative colitis they do not include digestion of the protective mucus coating of the stomach or colon.

METABOLISM OF HUMAN SERUM ALBUMIN IN MAN. *Richard D. Eckhardt, M.D. and Charles S. Davidson, M.D. Boston, Mass.* (From the Thorndike Memorial Laboratory, Second and Fourth Medical Services, Harvard, Boston City Hospital, and the Department of Medicine, Harvard Medical School.)

The metabolic fate of albumin was investigated by comparing the effects of its administration orally as whole protein and intravenously as whole and as completely hydrolyzed protein. Two normal and three undernourished subjects, maintained on constant 50 Gm. protein diets, received 50 or 75 Gm. of whole or hydrolyzed albumin daily for six days during six metabolic studies of from three to five weeks' duration.

The following results were obtained: (1) Hydrolyzed albumin given intravenously was promptly metabolized. Urinary nitrogen excretion increased immediately and remained constant throughout albumin administration and returned to the fore-control value the day it was discontinued. (2) During and after administration of whole albumin orally a three to five-day lag occurred before the urinary nitrogen excretion and nitrogen balance became constant. (3) When whole albumin was injected intravenously, the metabolism required approximately two weeks for completion as evidenced by the slow disappearance of albumin from the blood and delayed and gradual excretion in the urine as non-protein nitrogen. (4) The rate of disappearance of intravenously administered whole albumin from the blood was similar in normal and undernourished subjects. (5) Undernourished patients burned less administered whole albumin, whether given by mouth or by vein,

than did normals. (6) Most efficient utilization of albumin followed its administration intravenously as a whole protein.

It is concluded that albumin is available to both normal and undernourished subjects for metabolism regardless of its form or route of administration. The delay of approximately two weeks in reaching nitrogen balance when whole albumin is given intravenously reflects its slow degradation while the less marked delay following oral administration depends upon the time required to complete digestion and absorption. Nitrogen balance is promptly achieved when hydrolyzed albumin is administered intravenously since the processes of digestion and absorption or of degradation have been circumvented.

SODIUM AND POTASSIUM EXCRETION IN PATIENTS WITH RENAL INSUFFICIENCY. *Belton A. Burrows, M.D., Robert R. Commons, M.D. and Charles H. Burnett, M.D. (by invitation) Boston, Mass.* (From the Evans Memorial Hospital.)

The relationship between urine volume and sodium and potassium excretion has been studied under conditions in which changes in volume or electrolyte excretion were expected to occur. Normal subjects and patients with advanced renal insufficiency were given constant intakes of water but varying quantities of sodium or potassium while fasting. Also, consecutive voidings and consecutive twenty-four-hour collections were followed in patients with advanced renal insufficiency and in patients with acute renal failure.

In normal subjects changes in sodium and potassium excretion were gradual, although at times considerable and quite independent of wide changes in urine volume, with corresponding variations in urine concentrations. In the patients with advanced renal insufficiency under similar test conditions, urine volumes and concentrations and hence electrolyte excretions showed in general less variation as compared with the normal responses. The diurnal and day-to-day changes in the patients studied showed close correlation between urine volume and electrolyte excretion associated with almost constant urine concentrations, particularly of potassium. This urine electrolyte concentration was much higher in the patients with severe renal failure, acute or chronic, than has been observed in patients with normal renal function and minimal urine levels.

Several of the patients with high constant urine potassium concentrations had low serum potassium values. Administration of additional potassium resulted in a considerable uptake before the urine concentration rose. In most of these patients this constant urine potassium level lay between 20 and 35 mEq./L. in spite of two- or three-fold changes in urine volume. This suggests that patients with severe renal insufficiency probably are subject to loss of potassium as well as sodium in the urine.

QUANTITATIVE ESTIMATE OF VASOMOTOR TONE IN THE HUMAN EXTREMITY WITH COMPARATIVE STUDIES OF THE SYMPATHETIC BLOCKING AND ADRENOLYTIC PROPERTIES OF TETRAETHYLAMMONIUM, PRISCOL AND DIHYDROERGOCORNINE. *John W. Avera, M.D., Sibley W. Hoobler, M.D., Samuel G. McClellan, M.D. and William J. Little, M.D. Ann Arbor Mich.*

Presumably complete blockade of sympathetic vasomotor tone in the human subject without marked organic vascular disease was produced by means of spinal anesthesia, caudal anesthesia, lumbar paravertebral block or within twenty-four hours after sympathectomy. Blood flow to the foot as measured by the venous occlusion plethysmograph was regularly increased to an average of fourteen times control values. In contrast, tetraethylammonium (500 mg. intravenously) increased the blood flow on an average seven times the resting levels and produced no vasodilatation after sympathectomy or after intra-arterial administration. In usual clinical doses it therefore produced an approximately 50 per cent blockade of sympathetic vasoconstrictor tone and had no local vasodilator action.

Priscol (30 to 50 mg. intravenously) induced a three-fold increase in the blood flow in the foot and a two-fold increase in the innervated and denervated hand. The blood flow likewise was increased after intra-arterial injection. In this dosage the effects of the drug can in large measure be accounted for by a local vasodilator action although slight sympatholytic activity cannot be excluded.

Dihydroergocornine (0.25 to 1 mg. intravenously) caused a slow and delayed increase in the blood flow to 2.6 times the resting levels

in the foot and 2.1 and 2.4 times the resting levels in the innervated and denervated hand, respectively. In this dosage the drug has little or no sympatholytic effects and may produce vasodilatation after conversion into a vasodilator agent or by altering existing vasoregulatory mechanisms which are not mediated through sympathetic pathways.

Adrenolytic activity was measured by determining the effect of the drugs on the vasoconstrictor response to an intra-arterial injection of epinephrine. When tetraethylammonium, DHO or benzodioxane (16 mg.) were administered intravenously, the response to intra-arterial epinephrine was not altered. On the other hand, administration of priscol intravenously had a moderate adrenolytic effect. When high local concentrations of the last three drugs were achieved by intra-arterial injection, significant adrenalin blocking action was demonstrated.

Case Reports

Diffuse Progressive Interstitial Fibrosis of the Lungs*

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Cleveland, Ohio

We wish to report an unusual case of fatal pulmonary disease which presented at autopsy many of the features of acute diffuse interstitial fibrosis of the lungs, a disease first described by Hamman and Rich.[1] The clinical course of the present case differed from those which they described in that its duration was fifteen months instead of four to twenty-four weeks.

CASE REPORT

A. G., a single white thirty-two year old merchant seaman, was admitted to the U. S. Marine Hospital complaining of cough and shortness of breath. He was first admitted for this complaint on January 2, 1946. For three months before admission the patient had experienced some shortness of breath on exertion and for one month he had a cough which was productive occasionally of blood-streaked sputum and pain in the anterior chest.

Physical examination revealed nothing which was of any help in explaining the patient's symptoms. A roentgenogram of the chest (Fig. 1) showed hazy shadows in the lower half of the left lung and the lower fourth of the right immediately above the diaphragm. The heart and aorta were within the normal limits of size and contour. The roentgenologist considered these changes characteristic of atypical pneumonia. However, when a second roentgenogram made three weeks later showed no changes, a chronic, infection-producing pulmonary fibrosis was considered as another possibility. The laboratory studies which included repeated sputum examinations and blood studies added nothing to the solution of the problem. The patient was afebrile during his entire course of thirty-six days in the hospital. His shortness of breath improved and the cough disappeared.

His second admission to the hospital was on June 6, 1946, when he complained of symptoms similar to those experienced at the time of his first admission. After discharge from the hospital on February 7, 1946, he was free of symptoms until May when he had a return of his cough and shortness of breath which gradually grew worse until his second admission to the hospital.

The physical examination did not yield any more information at this time than it did at the first admission. His temperature was 37°C., pulse 90, respiration 22 and blood pressure 124/78. He was well nourished and did not appear acutely ill. There was a slight diminution in the intensity of the breath sounds at the base of the right lung. The heart was normal in size and no murmurs were heard. A roentgenogram of the chest showed only a slight change from that made five months previously. Streaky, fine, mottled shadows were present in both lung bases involving the lower half of the left lung and the extreme base of the right lung where there appeared to be an increase in the shadows. Since streaky and hazy shadows in both lung bases with little change on serial films had persisted for a period of five months, it was concluded that some chronic infection-producing fibrosis such as pneumoconiosis or sarcoidosis was responsible for these changes. The other laboratory studies added no information. The red blood cell count was 5,050,000, hemoglobin 12.2 Gm., white blood cell count 9,000 with 64 per cent neutrophils, 31 per cent lymphocytes and 5 per cent eosinophils. The sedimentation rate was 18 mm. per hour. The serologic test for syphilis was negative. The urine showed no abnormal findings; sputum examinations for

* From the Departments of Medicine and Pathology, U. S. Marine Hospital, Cleveland, O. Approved for publication by the Surgeon General, U. S. Public Health Service.

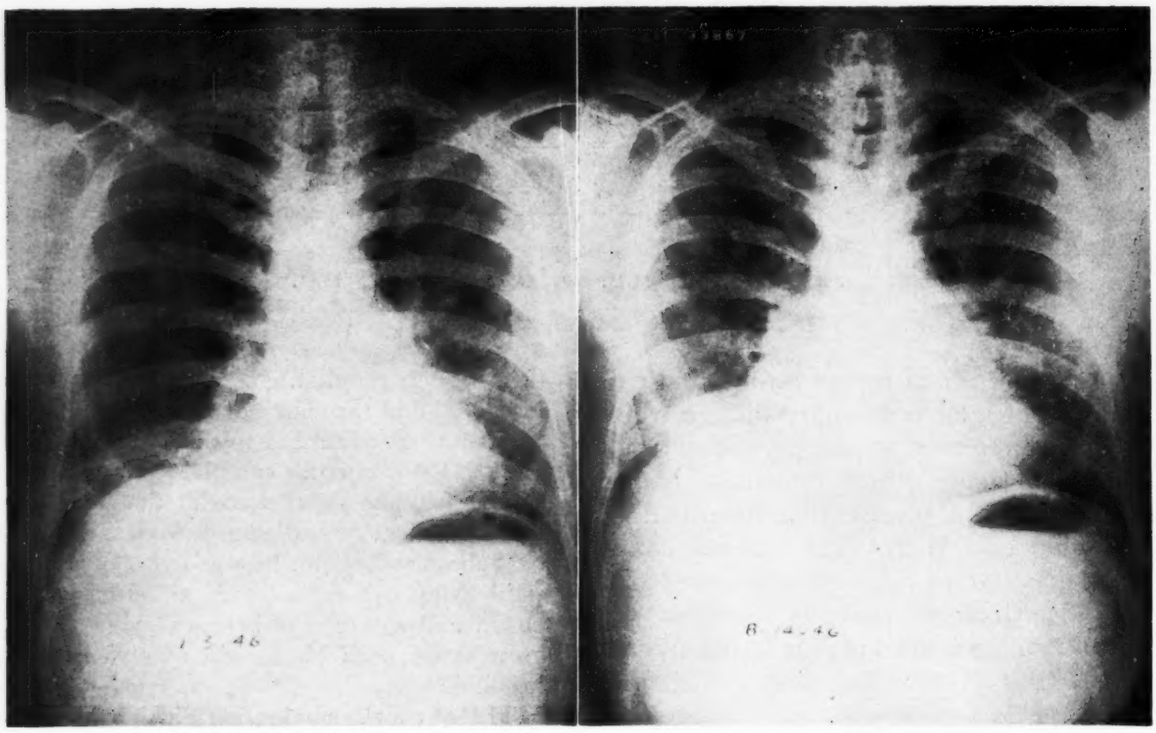

FIG. 1 FIG. 2

FIG. 1. Roentgenogram of the chest taken January 3, 1946, showing hazy shadows in the lower half of the left lung and the extreme base of the right.

FIG. 2. Roentgenogram taken August 14, 1946, showing an increase in the mottled and hazy shadows in both lungs. Changes noted in the contour of the heart and the prominence of the pulmonary vessels suggested cor pulmonale.

tubercle bacilli and for fungus infection were negative.

For the first nine weeks in the hospital the patient was ambulatory. During this time no change was noted except a slight increase in dyspnea. An x-ray of the chest made July 12, 1946, showed very little change from the one made a month previously. At the end of the tenth week in the hospital (August 8th) his dyspnea became much worse and a few rales were heard at the bases of both lungs. A systolic impulse and a diastolic impact were palpable over the right ventricle suggesting enlargement. A roentgenogram of the chest (Fig. 2) made August 14th showed progressive changes in the lungs with streaky, mottled and hazy shadows in the middle third of both lungs and upper third of the left lung just below the clavicle. Cor pulmonale was suggested by the increased prominence of the pulmonary vessels and filling of the incisura of the left upper border of the heart. On August 18th the patient's condition suddenly showed a marked change; his respiratory rate rose to 50 and he became extremely cyanotic. The only other changes which were noted at this time were a great increase in palpable precordial activity and more numerous rales at the bases of the lungs. Administration of oxygen by means of a tent produced a decrease in both the cyanosis and dyspnea. From this time until his death, December 12, 1946, he was never able to be out of the tent for more than thirty-minute periods. The cyanosis and dyspnea gradually increased in spite of oxygen therapy. There were no significant changes noted in the lungs but there was an increase in the palpable activity over the right ventricle; the pulmonic second sound was accentuated and the veins of the neck were distended. No other signs of cardiac failure were observed during the course of illness except for the last x-ray of the chest made November 18th at the bedside which showed dense, patchy, hazy shadows throughout both lungs suggesting pulmonary edema. The pulmonary vessels were very prominent and there was an increased bulging of the left upper border of the cardiac shadow. Another interesting development was clubbing of the fingers which was observed about four weeks after the cyanosis appeared. The only significant change in the laboratory studies was an increase in red cell count and

hemoglobin. The red cell count rose to 7,110,000 and the hemoglobin to 18.9 Gm. The white cell counts were normal throughout the illness until one month before death when they rose to 16,000. The patient remained afebrile until August 28th and then the temperature ranged from 37°C. to 38°C. until six days before death when it gradually rose, reaching a peak of 39.2°C. He died on the 189th hospital day. It was thought that the immediate cause of death was pneumonia.

The autopsy was limited to the chest. Some mucopurulent exudate coated the tracheal lining. No collection of fluid or pleural adhesions was found about the lungs. The left lung weighed 750 Gm. and the right 850 Gm. The upper lobes of the lungs presented the appearance of an almost uniform pneumonic consolidation. A deep, reddish color prevailed on the cut surface of the left upper lobe and a mottling of greyish and brownish areas appeared on the right side. The lower lobes indicated an uneven firmness to palpation; firm, greyish and somewhat granular areas were distributed throughout these lobes on section. Frequent areas of emphysema were enclosed by the interlacing, dense, fibrotic portions of the lower lobes and groups of emphysematous blebs occurred at peripheral locations. (Fig. 3.) An exudate was expressible from frequent bronchi. No thrombi were observed in the blood vessels.

The histopathologic findings were much the same as those described in the cases of Hamman and Rich, an opinion confirmed by Dr. A. R. Rich. Microscopically, a widespread interstitial fibrosis was noted in all lobes. The left upper lobe showed considerable obliteration of the normal alveolar spaces due to pronounced thickening and some hydropic changes of the alveolar walls. Many dilated capillary blood vessels occupied most parts of the walls of the alveoli and some proliferation of fibroblasts was noted about these vessels. Strips of fibrinohyaline membranes were conspicuous in or about frequent alveoli and some of the air vesicles contained clumps of fibrin, leukocytes and desquamated epithelial cells or collections of red corpuscles. (Fig. 4.) In the lower half of the lobe there was a gradual change from the congestion and prevalence of capillary vessels to a very unusual and pronounced proliferation of connective tissue in and about the alveolar walls which was true in all of the other lobes. There were widely distributed beady or patchy

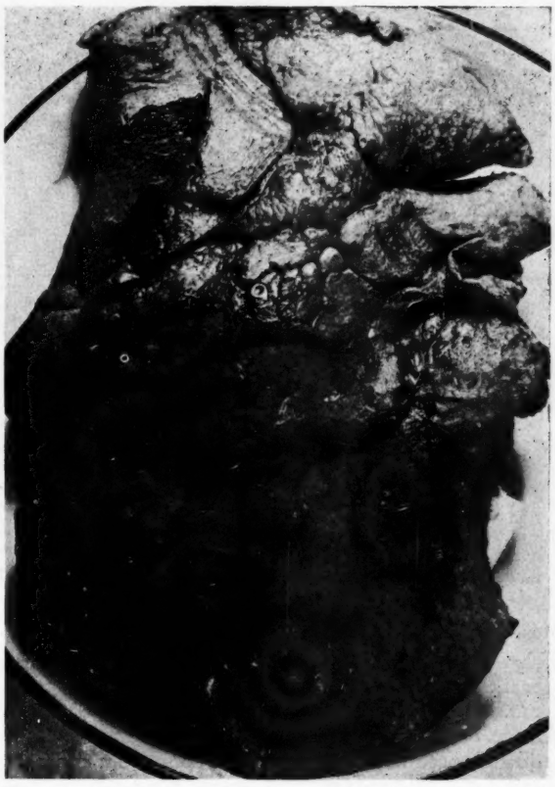

FIG. 3. An almost uniform consolidation is exhibited on the cut surface of the upper lobe. The firmness of the lower lobe is interrupted by frequent foci of emphysema. Several borders of the lobes show emphysematous blebs.

fibrotic areas and partial obliteration of the alveolar spaces. The epithelium of the alveoli frequently was composed of prominent, high epithelial cells, some of which were unusually large, causing the epithelium to be irregular in places. (Fig. 5.) Occasionally parts of the alveolar epithelium were absent and in some regions the nuclei of the epithelial cells were indistinct or fragmented.

A number of bronchi contained some fibrinocellular exudate. In very occasional parts of the bronchi or bronchioles the epithelium was vacuolated or indistinct and the lumina of some of the small bronchi were narrowed or obliterated. The linings of several bronchi showed squamous-celled metaplasia and, rarely, minute peripheral spots of heteroplastic ossification occurred in lung sections. The interstitial areas were frequently seats of small groups of lymphocytes, pigment-bearing phagocytes, loose collections of histiocytes and plasma cells, scattered giant cells and eosinophiles. In addition, frequent groups of dilated capillary vessels were noted and islets of large, epithelial-type cells were

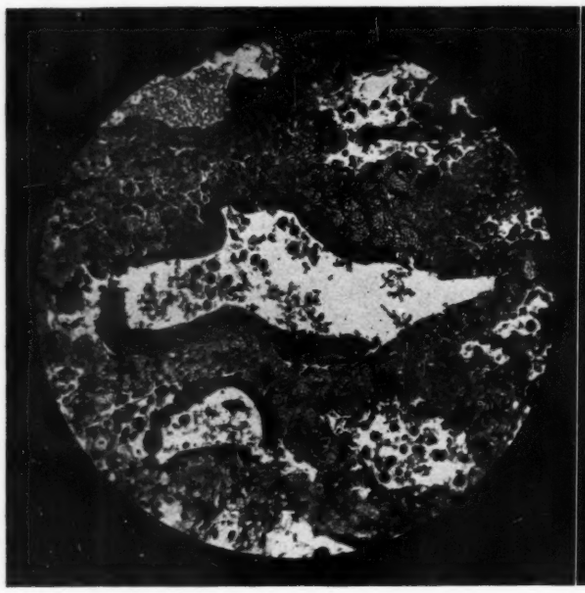

FIG. 4

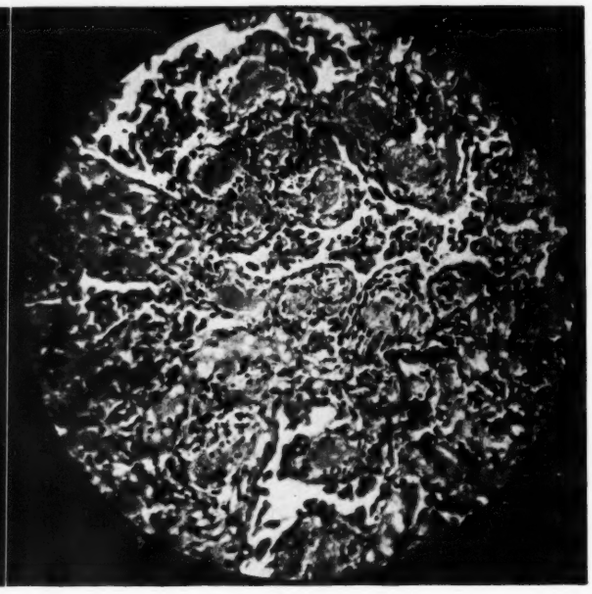

FIG. 5

FIG. 4. A field from the upper lobe of the left lung which shows greatly thickened alveolar walls occupied by dilated capillary vessels. Note the loose collections of wandering cells, incipient proliferation of fibroblasts and hyaline membranes lining alveolar spaces; × 210.

FIG. 5. Advanced proliferation of connective tissue is seen in and about the alveolar walls with much narrowing of the alveoli in the upper half of the field. Note the beady character of the fibrosis in the upper half of the field, the frequently prominent alveolar lining epithelium and heaping of epithelial cells; × 210.

conspicuous in several sections; however, we believe that these heaps of cells were within deformed or collapsed air vesicles or represented proliferations of the alveolar epithelium. Focal emphysema involving a considerable number of alveoli was a conspicuous finding, especially in the lower pulmonary lobes. The branches of the pulmonary arteries indicated no intimal thickening of significance. The tracheobronchial lymph nodes were congested and enlarged; microscopically, occasional collections of mononuclear and plasma cells were present in the sinuses.

The heart was moderately enlarged and somewhat flabby in consistency; it weighed 470 Gm. The right ventricle was dilated and its musculature indicated hypertrophy, showing an average thickness of 6 mm. The left ventricle measured 12 mm. in thickness. The valves and the coronary vessels showed no remarkable lesion and the microscopic appearance of the myocardium was essentially normal. A mild intimal sclerosis of the aorta was noted.

COMMENTS

The pathologic studies indicate that the proliferative fibrotic process was most advanced in the lower lobes while parts of the upper lobes presented a more recent lesion. The histologic sections of the case reproduced most of the pathologic peculiarities described by Hamman and Rich, as follows: (1) There was a diffuse and progressive interstitial proliferation of connective tissue throughout all lobes of both lungs; this tissue production showed varying stage of development and activity. A rather moderate degree of inflammation, recent and old, was noted; however, it differed from lesions present in ordinary pneumonia of bacterial origin. For analogy we quote Rich: "The essential peculiarity in this condition is the remarkable proliferation of connective tissue that occurs within the alveolar walls, even in the absence of the organizing exudate in the related alveolar spaces. One can find virtually all stages of the process, from the acute inflammatory phase, to complete fibrosis. It is quite clear that the attack on the lungs in this condition does not begin everywhere at once, but rather, spreads from place to place until all lobes of both lungs have become diffusely

involved with lesions in different stages of development." (2) a proliferation of capillary blood vessels and hydropic changes were noted at places in the alveolar walls; hyaline membranes lined the alveoli and a moderate degree of inflammation was observed. (3) Proliferation and prominence of the lining alveolar epithelial cells, frequently resembling the bronchiolar epithelium, were present. (4) There was stenosis of some small bronchi and bronchioles with emphysematous dilatation of the adjacent alveoli. (5) No stainable bacteria were demonstrated in the pulmonary parenchyma and a smear of the bronchial exudate showed pairs of gram-negative and gram-positive cocci. The only differences noted in the histologic examination from those described in the cases of Hamman and Rich were that there were less edematous changes; no striking numbers of eosinophilic cells were found; the necrosing changes in the alveolar and bronchial epithelium were infrequent; and the thickening of the alveolar walls frequently exhibited a remarkable beady appearance.

In this case the clinical course can be divided into two stages; first, a latent period of eleven months and second, an active phase of four months. During the first ten and one-half months of the latent period very little progression of the disease was noted. There were no physical findings during this time to explain the shortness of breath and cough; however, the roentgenogram showed changes at the bases of both lungs which suggested pulmonary fibrosis. In the last two weeks of this period the dyspnea became worse; a few rales were heard at the bases of both lungs and cor pulmonale was suggested by the increased palpable activity of the right ventricle and the roentgenologic changes noted in the cardiac shadow.

The active phase of the disease began abruptly and followed a course similar to those described by Hamman and Rich and Eder, Hawn and Thorn.[2] This sudden change, manifested by cyanosis and marked dyspnea which was never completely relieved by oxygen therapy and gradually became worse over a period of four months, could not be explained adequately by any changes found in the lungs. The sudden onset suggested heart failure; however, the only signs indicating this were an increase in precordial activity, distention of the veins of the neck and the changes in the roentgenogram made one month before death which suggested pulmonary edema.

The histologic changes found in the lungs offer an explanation for the failure of oxygen to give the expected relief of the dyspnea and cyanosis and the disparity between the subjective symptoms and the physical findings in the lungs. A great increase in the connective tissue was noted in the alveolar walls which must have completely obstructed the exchange of gases in the alveoli where the process was well-advanced. As the respiratory membrane of the lung was reduced the dyspnea and cyanosis increased and the response to oxygen administration became less. In addition to interfering with the exchange of gases a reduction of the pulmonary vascular bed occurred producing an increase in pressure in the pulmonary artery resulting in cor pulmonale. The great disparity between the subjective symptoms and physical findings is easy to understand since the pathologic changes were confined chiefly to the alveolar walls.

SUMMARY

1. An unusual case of fatal pulmonary disease has been presented. The clinical and pathologic aspects have been discussed.

2. This case differed from those described previously in that the duration of the disease was fifteen months instead of four to twenty-four weeks.

3. Observation of the course of the disease throughout the latent period of eleven months and the active period of four months offered us an opportunity to observe the development of cor pulmonale, clubbing of the fingers and polycythemia.

4. In view of the longer duration of the disease in this case we propose to employ

the term "diffuse, progressive, interstitial fibrosis of the lungs."

We wish to thank Doctor Carol Dundon for his cooperation and interest in the interpretation of the x-ray films and Doctor Herbert Z. Lund for his helpful suggestions in the pathologic studies.

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A Syndrome Characterized by Generalized Cutaneous Eruption, Chorioretinitis and Eosinophilia, Probably Due to Chronic Toxoplasma Infection*

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INFECTION with toxoplasma parasites can produce a variety of clinical syndromes in man. This obligate intracellular protozoan has been shown to be the cause of a congenital encephalomyelitis of the newborn,[1] an acute encephalitis in children,[2] a typhus-like syndrome of adults associated with pneumonitis,[3] an acute febrile illness in adults clinically similar to trichinosis[4] and non-apparent infections in adults detected by finding circulating antibodies against this parasite.[5]

It is the purpose of thispaper to describe a heretofore unreported type of chronic illness characterized by the presence of a generalized cutaneous eruption, chorioretinitis and eosinophilia. Antibodies against toxoplasma were present in the blood of the patient and a positive skin test was obtained when toxoplasma antigen was injected intradermally into this individual. However, several attempts to isolate toxoplasma from the patient's blood, sternal marrow and spinal fluid were unsuccessful.

CASE REPORT

A white male, aged thirty, was admitted to the Veterans Administration Hospital, Washington, D. C., on September 24, 1947. He had been a well-driller prior to military service. There was no history of prolonged contact with animals or arthropods. In 1943 the patient developed a bilateral iritis together with symptoms of anorexia and severe epigastric pain which were unrelated to intake of food and not relieved by medication. Roentgenograms showed the duodenum to be irregular and there was evidence of crater formation on its superior and anterior wall. He was discharged from the service in 1943 with a diagnosis of duodenal ulcer. These symptoms persisted until the present hospital admission. In December, 1945, tender nodules varying in diameter from a few mm. to 5 to 6 cm. began to appear under the skin. They usually occurred in crops and persisted for four to six weeks and then gradually subsided. The nodules at various times have appeared over the entire body including the soles of the feet and the scalp. Crops of small vesicles varying from 2 to 4 mm. in diameter and containing clear fluid were also noted. The vesicles promptly became hemorrhagic and were the sites of intense pruritus. Dark brown scabs formed following rupture of the vesicles and after several weeks these scabs separated from the skin surface, leaving reddened areas which eventually faded but left atrophic scars similar to the residual lesions of smallpox. Nodules and vesicles of this type recurred continuously from 1945 to 1948. Pain was often present in the lower extremities from the onset of this illness. In addition the patient complained of weakness, severe headache, loss of weight and intermittent fever. There was a history of two attacks of Bell's palsy, the first involving the right side in July, 1944, and the second occurring on the left in March,

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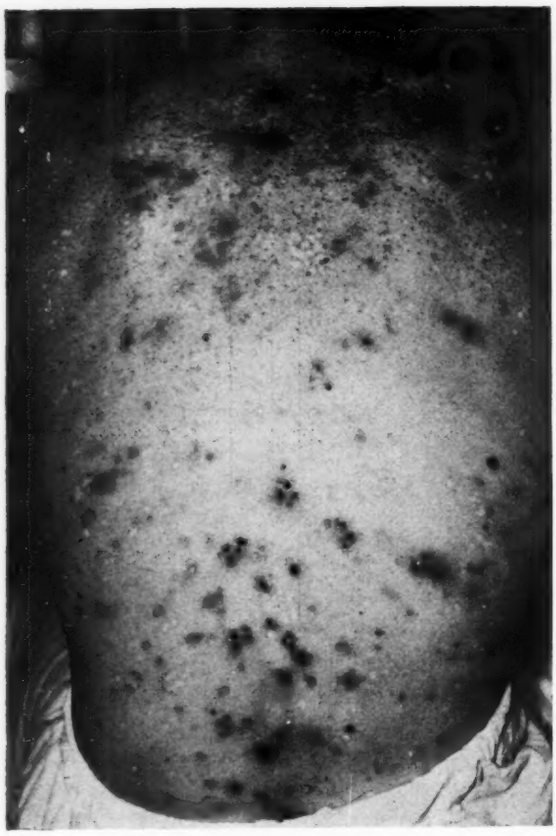

FIG. 1. Appearance of patient on November 25, 1947.

1947. There was complete recovery from each attack. A biopsy of a subcutaneous nodule was taken three months before entering Veterans Administration Hospital. On the basis of its histopathology a diagnosis of dermatomyositis was made.

Physical examination revealed the patient to be a well developed, fairly well nourished white male who nevertheless appeared chronically ill and older than his stated age. His hair was prematurely gray. Examination revealed an old area of chorioretinitis approximately the size of the optic disc in the periphery of the left fundus, a small ulcerative lesion about 5 mm. in diameter on the right tonsil and multiple, raised, tender, erythematous, subcutaneous nodules scattered diffusely over the trunk and extremities. In addition, innumerable cutaneous lesion were present. These were in various stages of development from vesicles with crusted surfaces to erythematous and non-erythematous scars of varying size. (Fig. 1.) No other abnormalities were noted in the physical examination.

Clinical laboratory data was as follows: Blood count on admission: red blood cells, 4,600,000; hemoglobin, 14 Gm.; white blood cells, 11,150; polymorphonuclears, 74; lymphocytes, 19; monocytes, 3 and eosinophiles, 4. The sedimentation rate was 30 mm. in one hour corrected (Wintrobe). Throughout the hospital stay the red blood cells ranged between 4,040,000 and 4,630,000, white blood cells between 5,900 and 11,150. There was little change in the differential counts except for an eosinophilia which reached 14 per cent. Urinalysis on admission: specific gravity, 1,022; albumin, very faint trace; sugar, negative; microscopic examination, 10 to 20 white blood cells, 8 to 10 red blood cells and a few hyaline and fine granular casts. Subsequent urinalyses were within normal limits except during a period of therapy when numerous red blood cells and sulfadiazine crystals were seen. The cytology of the sternal bone marrow was normal. All bacteriologic studies were negative. A complement fixation test for histoplasmosis was positive to a titer of 1:32 in one instance but on repeated examination one month later was negative. Intravenous phenolsulfonphthalein, urea clearance and Fishberg concentration tests were within normal limits. X-ray examinations of the skull, chest and gastrointestinal tract were negative. Oscillometric readings of the lower extremities were within the normal range. There were no electrocardiographic abnormalities.

A biopsy of a skin lesion and subcutaneous nodule was taken on September 25, 1947. The histologic findings were not pathognomonic for any pathologic entity. The tissues revealed infiltrations with numerous eosinophiles; severe vascular changes were also present and suggested a so-called "hyperergic" type of inflammation. (Fig. 2.) Toxoplasma were not observed in a careful examination of numerous sections of this material.

Three attempts were made to isolate toxoplasma from the patient's blood. On October 21, 1947, heparinized blood was injected intracerebrally and intraperitoneally into each of ten mice and two guinea pigs. On November 5, 1947, a second specimen of blood was obtained and inoculated into the chorio-allantoic sac of ten embryonated eggs, and into two guinea pigs by the intradermal and intraperitoneal routes. Spinal fluid also taken at this time was injected into ten embryonated eggs. The third attempt at isolation was performed on November 24, 1947, when 25 cc. of heparinized blood was centrifuged at 3,500 revolutions per minute for twenty minutes and the sediment resuspended

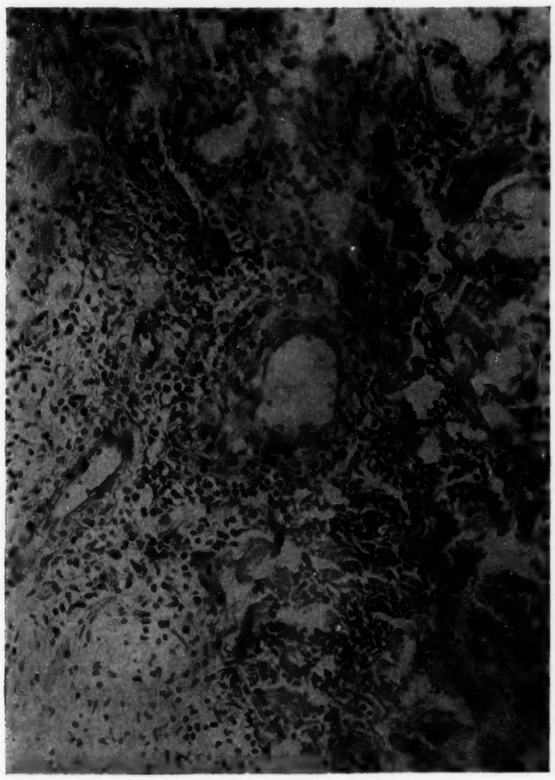

FIG. 2. Section through a biopsied portion of a cutaneous lesion; × 300.

in 5 cc. of physiologic saline solution. This material was then inoculated intraperitoneally into mice, guinea pigs and into the chorio-allantoic sac of embryonated eggs. At this time also sternal marrow was aspirated from the patient and injected into mice and guinea pigs.

None of these inoculations produced any signs of disease in the animals or embryonated eggs. Furthermore, serial blood passages which were performed in a number of instances also gave negative results. The failure of the guinea pigs to develop specific complement-fixing antibody of toxoplasmosis indicated the absence of even subclinical infection.

Complement fixation tests were performed to determine the toxoplasma antibody level in the patient's serum taken on October 19, 1947 and November 5, 1947. Both serum specimens fixed complement at a dilution of 1:128 when tested with toxoplasma antigen prepared from infected chorio-allantoic membrane.[6] Furthermore, both sera gave strongly positive reactions in neutralization tests carried out in rabbits inoculated intradermally.

On the basis of these positive serologic reactions it was decided to perform an intradermal skin test on this patient, employing an antigen

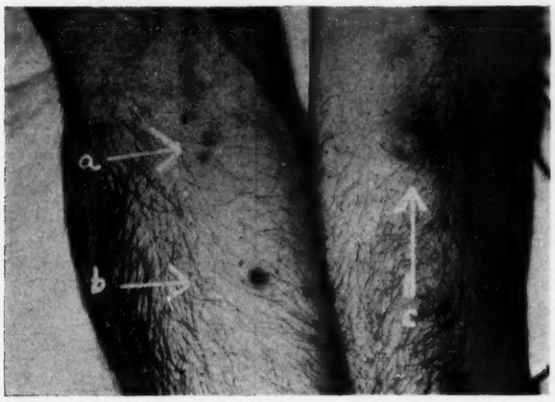

FIG. 3. Appearance of toxoplasma skin test forty-eight hours after inoculation. Toxoplasma antigens injected into left forearm, control on right arm; *a*, control; *b*, spontaneous lesion; *c*, induced lesion.

derived from toxoplasma-infected chorio-allantoic membrane.[6] The antigen was prepared as follows: A 10 per cent suspension of infected membranes in physiologic saline solution was rapidly frozen and thawed three times to destroy the toxoplasma and then centrifuged at 3,000 revolutions per minute for fifteen minutes. The supernatant fluid was removed and sufficient merthiolate added to make a final concentration of 1:10,000. After this material had been shown to be bacteriologically sterile and non-infectious for mice and guinea pigs it was used as a skin test antigen. A suspension of normal chorio-allantoic membrane prepared in a similar fashion served as a control antigen. On November 24, 1947, the patient was inoculated intradermally with 0.1 cc. amounts of 1:1,000 and 1:100 dilutions of the control and toxoplasma antigens. There was no immediate reaction at either site. Sixteen hours later a slight reaction was noted at the site of the injection of the 1:1,000 dilution of toxoplasma antigen and a raised erythematous area measuring 1.0 by 1.0 by 0.2 cm. at the site of the injection of the 1:100 dilution of toxoplasma antigen. Forty-eight hours following the skin test the site of the 1:100 dilution measured 1.5 by 1.5 by 0.3 cm. (Fig. 3.) At this time the lesion became pruritic and a small vesicle appeared which was indistinguishable from the cutaneous lesion previously described on the patient. Seventy-two hours after injection the lesion had become slightly discolored and hemorrhagic in appearance, resembling a spontaneous cutaneous lesion. No visible reactions were present at the control sites. Examination of a biopsy specimen of the skin obtained from the site of injection of

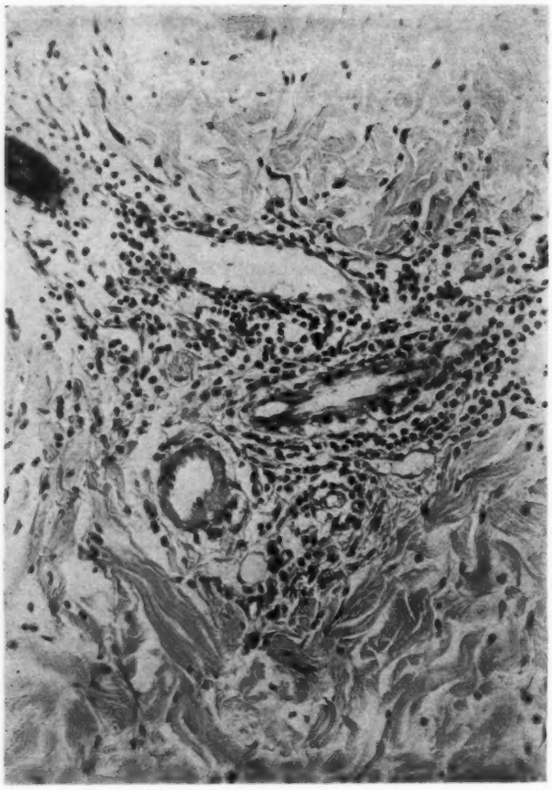

FIG. 4. Section through a biopsied portion of an induced skin lesion resulting from the intradermal inoculation of an extract of toxoplasma-infected chorio-allantoic membrane; × 300.

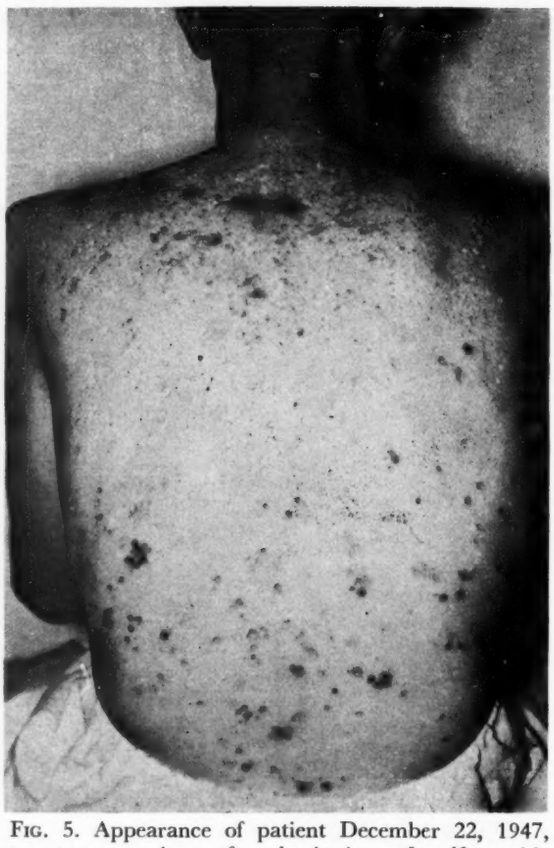

FIG. 5. Appearance of patient December 22, 1947, twenty-seven days after beginning of sulfonamide therapy.

the 1:100 dilution of toxoplasma antigen on the ninth day after inoculation revealed a histologic picture (Fig. 4) similar to that of the spontaneous skin lesion.

From the date of admission until November 25, 1947, the patient's symptoms persisted unabated. His temperature ranged from 98.6°F. to 102.0°F. and during this period he was afebrile on only three occasions which lasted five days, two days and three days, respectively. He was seen by a dermatologist who indicated that the skin eruption was compatible with the diagnosis of erythema multiforme bullosum. Because of the data suggesting a diagnosis of toxoplasmosis, and in light of the experimental work done by Sabin and Warren on the use of certain sulfonamides in the treatment of laboratory animals infected with toxoplasma,[7] sulfadiazine therapy was instituted on November 25, 1947, using 6.0 Gm. daily. For ten days prior to the initiation of therapy the patient's temperature ranged from 98.6°F. to 101.8°F. Within twenty-four hours after administration of sulfadiazine the patient's temperature dropped to normal and he remained afebrile for a period of twelve days. The muscular and epigastric pain markedly decreased in severity and duration, his appetite improved, the headaches disappeared and there was a marked decrease in the formation of new nodules and vesicles. (Fig. 5.) Prior to therapy he required analgesic drugs for the relief of pain but none were necessary during this afebrile period.

On December 5, 1947, the patient had a sulfadiazine level of 20.2 mg. per cent. Because of this high level therapy was discontinued for twenty-four hours. At the end of this interval the level had dropped to 13.8 mg. per cent and sulfadiazine was again instituted but with the dose reduced to 4.0 Gm. per day. In spite of continued medication the patient's temperature again became elevated, ranging between 99°F. to 100.6°F. for two days, following which he was essentially afebrile for thirteen days. At this time (December 27, 1947), he developed hematuria which necessitated discontinuance of sulfadiazine. Following this his symptoms, with the exception of epigastric pain, reappeared but his temperature ranged between normal and 99.5°F. The rate of formation of new nodules and vesicles

returned to the pretreatment level. On January 17, 1948, the therapy was modified and sulfapyridine alone, 1 Gm. daily, was started and increased to 2 gm. daily on January 28, 1948. It then became imperative for him to leave the hospital for personal reasons and he was discharged on February 2, 1948. Correspondence received from the patient on June 3, 1948, indicated that his condition was similar to that on admission.

COMMENTS

The rather bizarre clinical features observed in this patient suggested several possible diagnoses: among these were periarteritis nodosum, erythema multiforme and toxoplasmosis. All but the latter were discarded when the positive serology for toxoplasma was discovered.

It seemed to us not unlikely that this man's present illness probably dated back as far as 1943 at which time a diagnosis of duodenal ulcer and bilateral iritis was made. The occurrence of two episodes of Bell's palsy, first in 1944 and again in 1947, suggested that injuries to the central nervous system might have occurred at or shortly after the appearance of iritis and the cutaneous lesions previously noted.

The finding of strongly positive complement fixation, neutralization and skin sensitivity tests for toxoplasma made it possible to account for many of the puzzling features of this case. The chorioretinitis, headache and fever are in accord with the pathologic changes known to be caused by this parasite. Toxoplasma are transported in the blood stream and invade and multiply in any of the mesenchymal tissues of the body. Their final localization is apparently determined by: (1) chance, (2) mechanical effects, as the filtering action of the lung and spleen and (3) factors as yet unknown. It is not unlikely that this non-selective localization accounts for the varied manifestations often observed in human toxoplasmosis. The long duration of illness in our patient also has a parallel in the well established fact that chronic toxoplasmosis exists in animals[1] and it is most probable that a chronic infection exists for a considerable time in the mothers of infants who are born with congenital toxoplasmosis.[5]

The case described in the present report is distinguished by an eosinophilia and the appearance of crops of nodular or vesicular lesions involving the epidermis and subcutaneous layers of the skin. Although no parasites were observed in the tissue at these sites, the histopathology of these nodules is essentially identical with the response elicited by the intradermal inoculation of a toxoplasma antigen. The histologic picture is also similar to that induced by the injection of any reagin into a hyperergic individual.[10] It is our opinion that the continued appearance of these cutaneous lesions is due to the constant release of living toxoplasma or toxoplasma antigen from one or more internal foci. These parasites, finding their way into the smaller capillaries, evoke an allergic reaction in this individual but in the presence of the high level of humoral antibody are unable to multiply to any extent and the cutaneous lesion eventually recedes. The repeated failure to isolate toxoplasma from this patient will be raised as an argument against this hypothesis. However, it should be noted that the number of circulating parasites even in heavily infected experimental animals is often small.[9] Furthermore, it will be recalled that several cases of human toxoplasmosis have been reported in which toxoplasma could not be isolated from the blood or spinal fluid.[11a,b]

Following administration of sulfadiazine this patient exhibited marked improvement in his general condition. After twenty-two days of this therapy he unfortunately developed hematuria which made it necessary to discontinue the drug. His subsequent course has not been improved. Unfortunately no alternative therapeutic agents to the sulfonamides are presently available for the therapy of human infection from toxoplasma.

SUMMARY

The case of a thirty year old male exhibiting generalized cutaneous eruption,

chorioretinitis and eosinophilia of three years' duration is described. Serologic tests and an intradermal skin test for toxoplasmosis were strongly positive. Sulfonamide therapy was beneficial but the appearance of hematuria necessitated discontinuance of the drug. Following this the patient's condition deteriorated. The possible etiology of this case is discussed.

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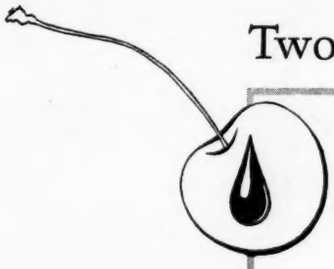

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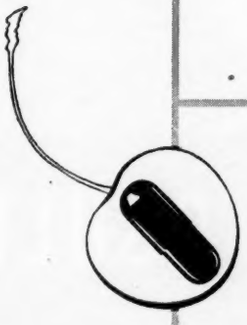

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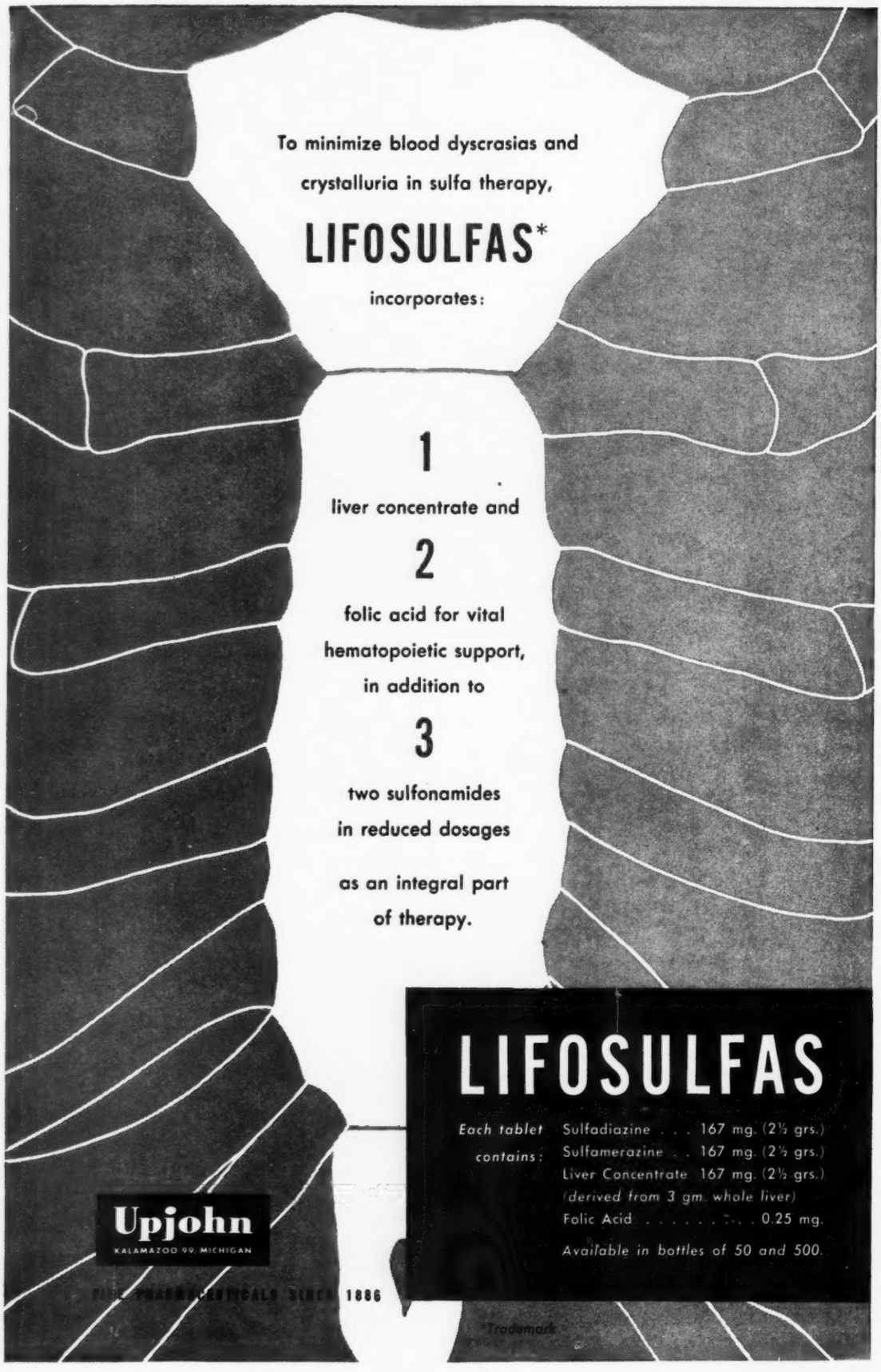
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1. Brewster, J. M., U. S. Naval Med. Bull. **49**: 1-11, January-February 1949.

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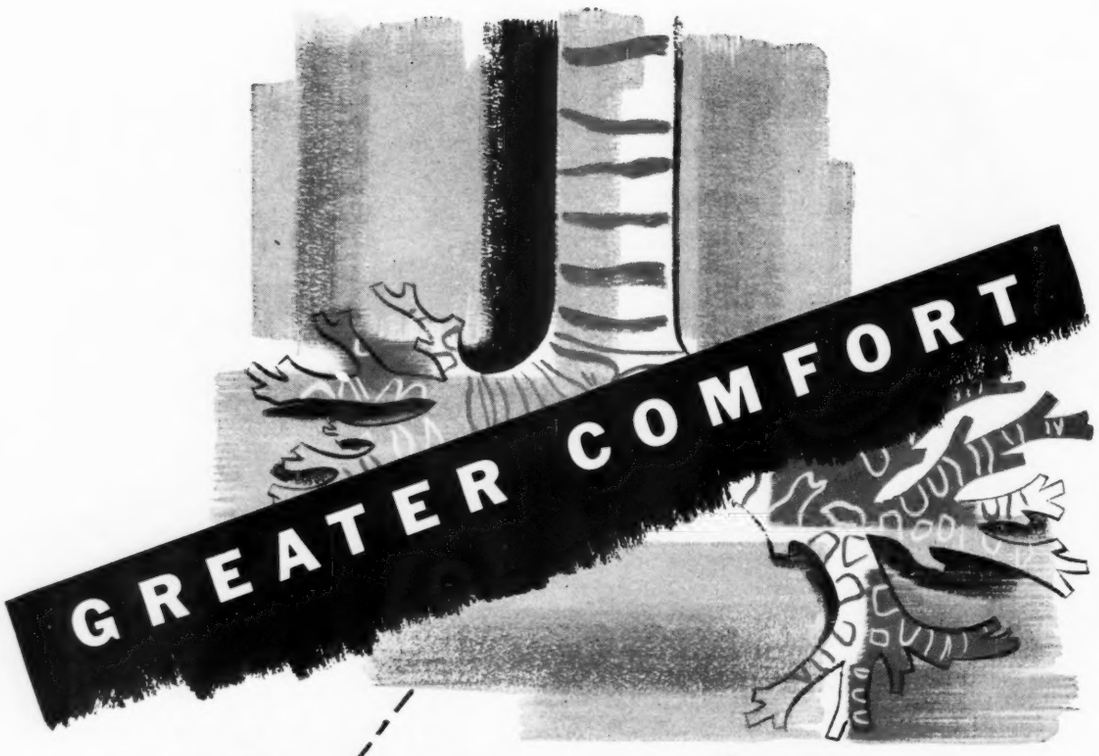

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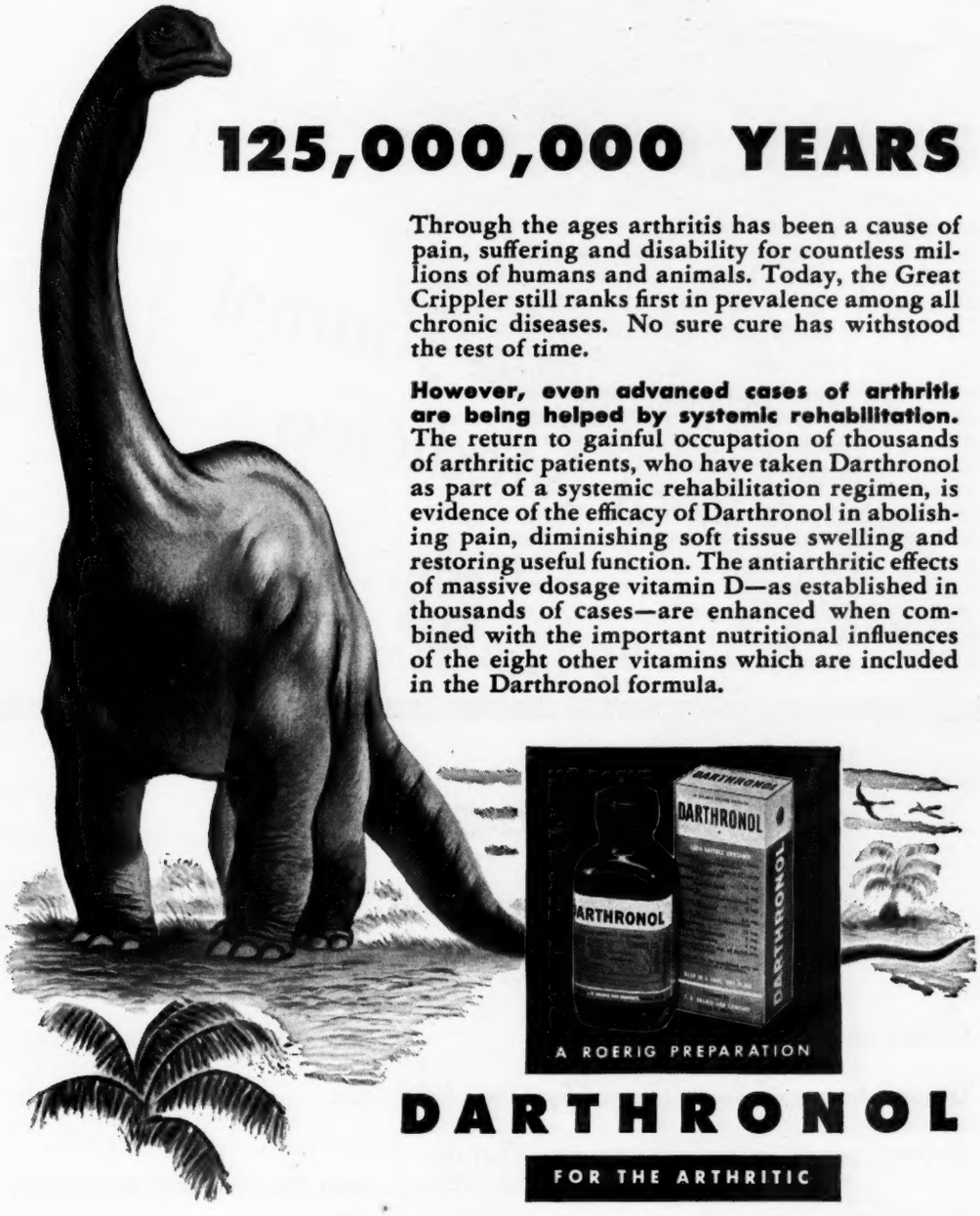

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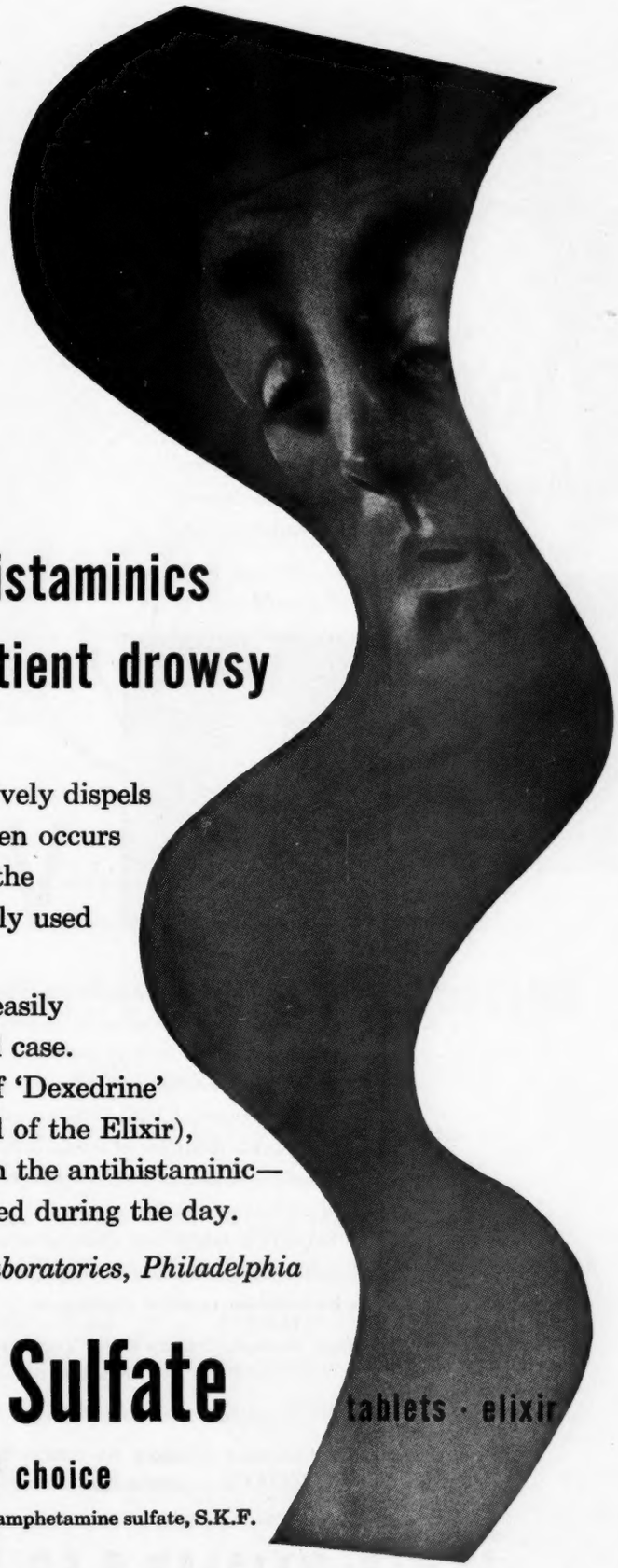

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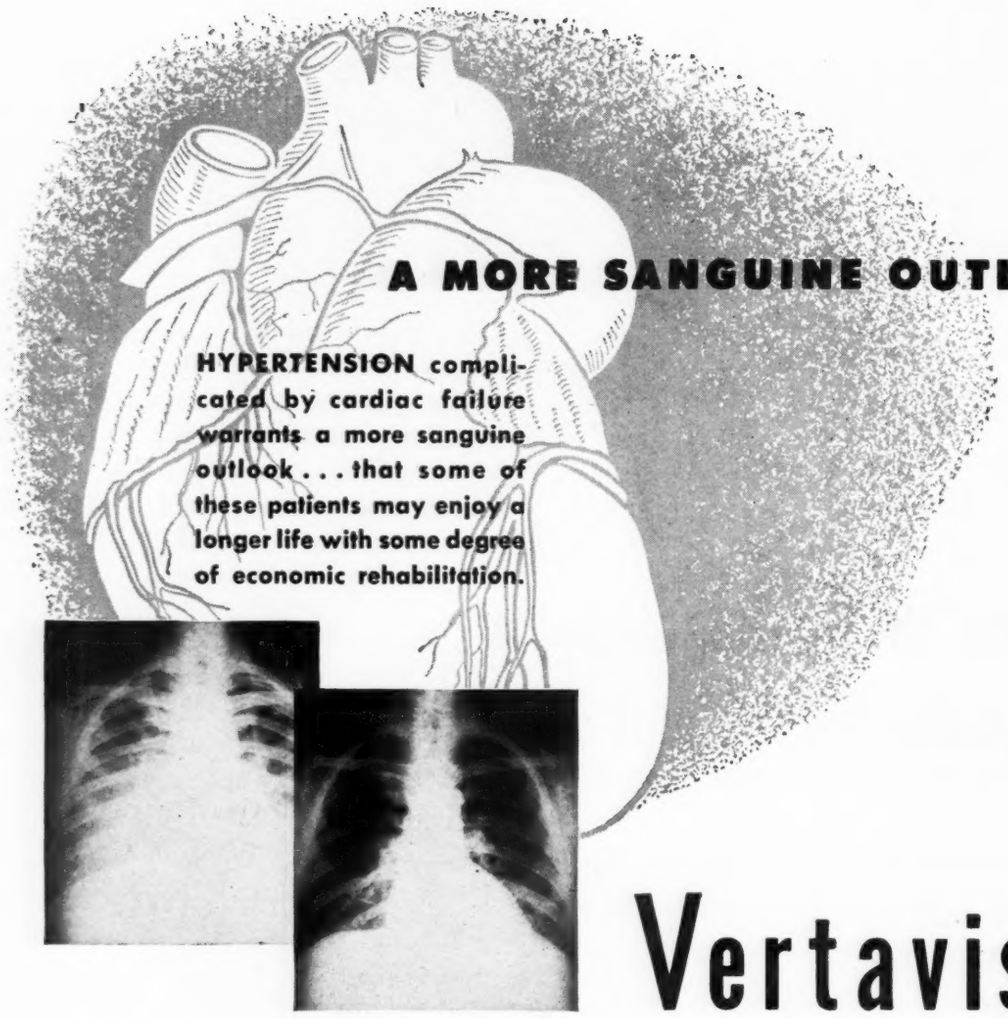

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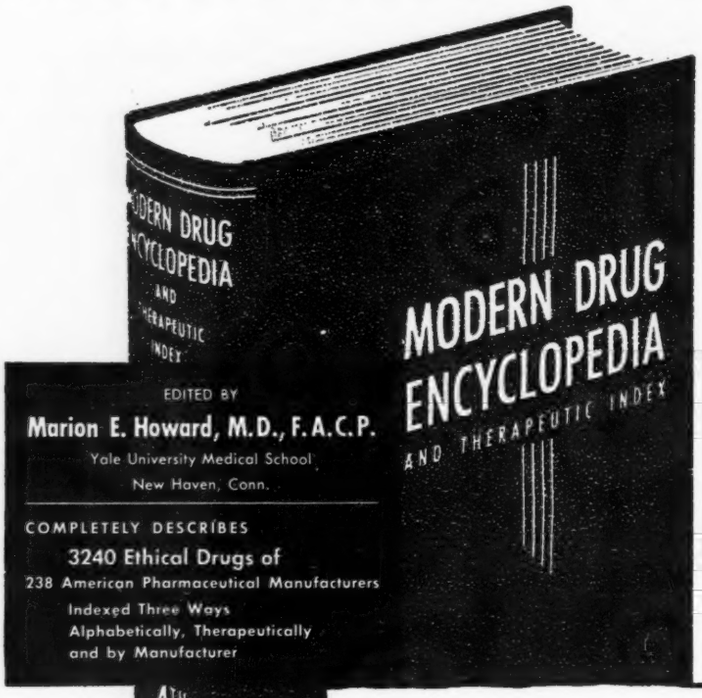

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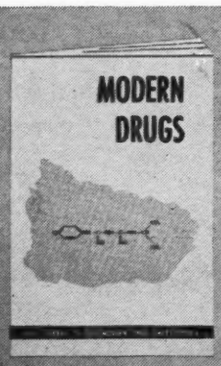
ACTION AND USES: Effects an adequate hematopoietic response in pernicious anemia cases; offers a substitute for liver therapy in the treatment of pernicious anemia patients who exhibit a sensitivity to liver extract. An important adjunct to liver therapy in the treatment of pernicious anemia, nutritional macrocytic anemia, non-tropical sprue and tropical sprue.

ADMINISTRATION: *Intramuscularly,* preferably in the gluteal muscle. In macrocytic anemia of pregnancy, 10 to 20 micrograms once a week until termination of pregnancy. In macrocytic anemia of infancy, 10 to 20 micrograms until blood count returns to normal. In nutritional anemia dosage may vary from 6 to 100 micrograms over a 14 day period to obtain an optimal response. In most pernicious anemia cases 25 micrograms per week results in an optimal response.

SUPPLY: B_{12} CONCENTRATE—Vials, rubber-capped, 10 cc.



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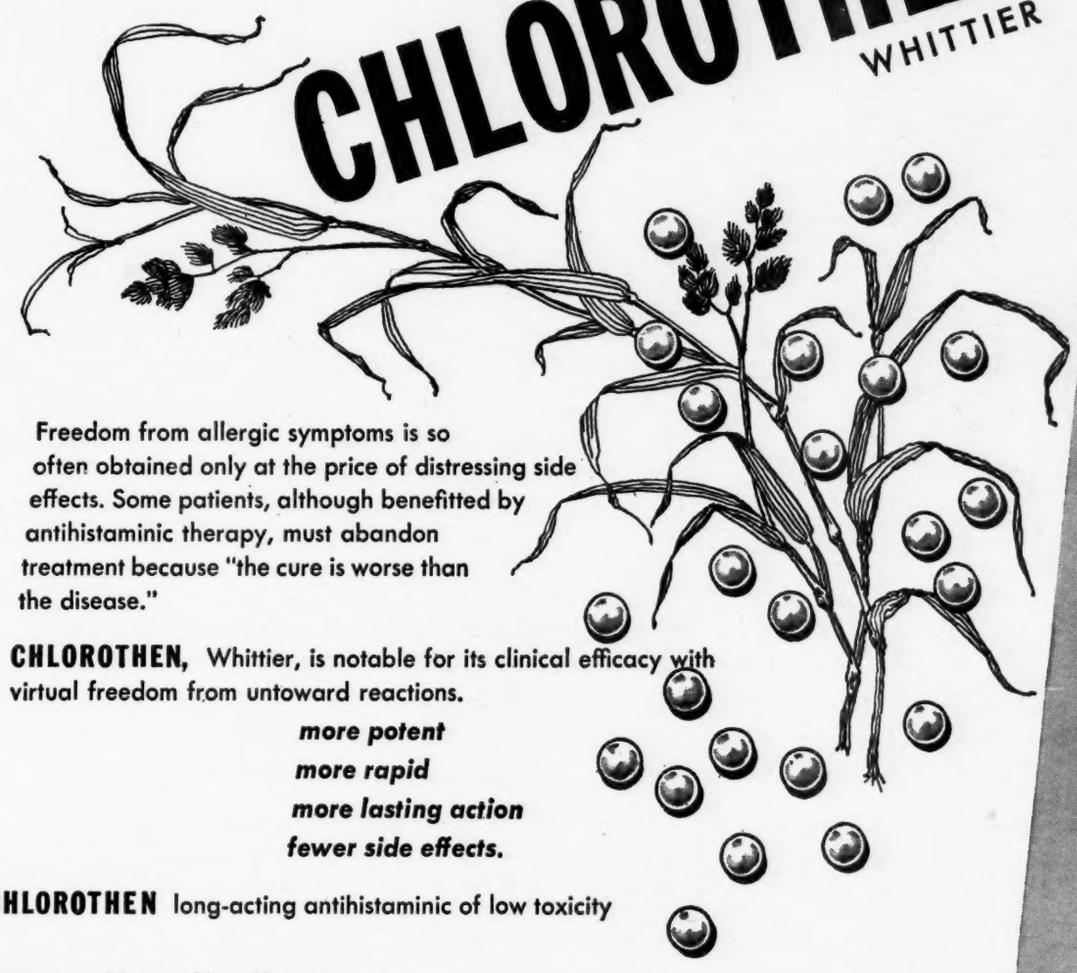

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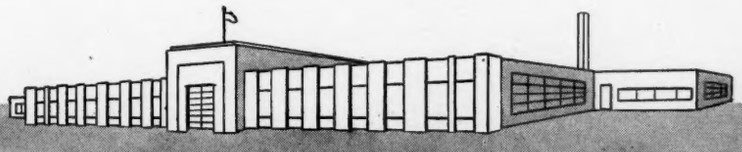

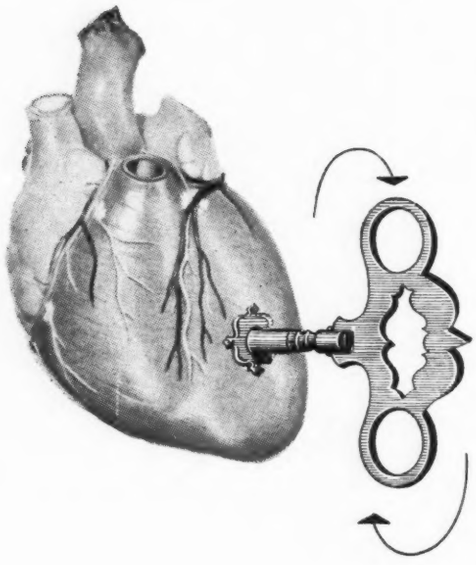

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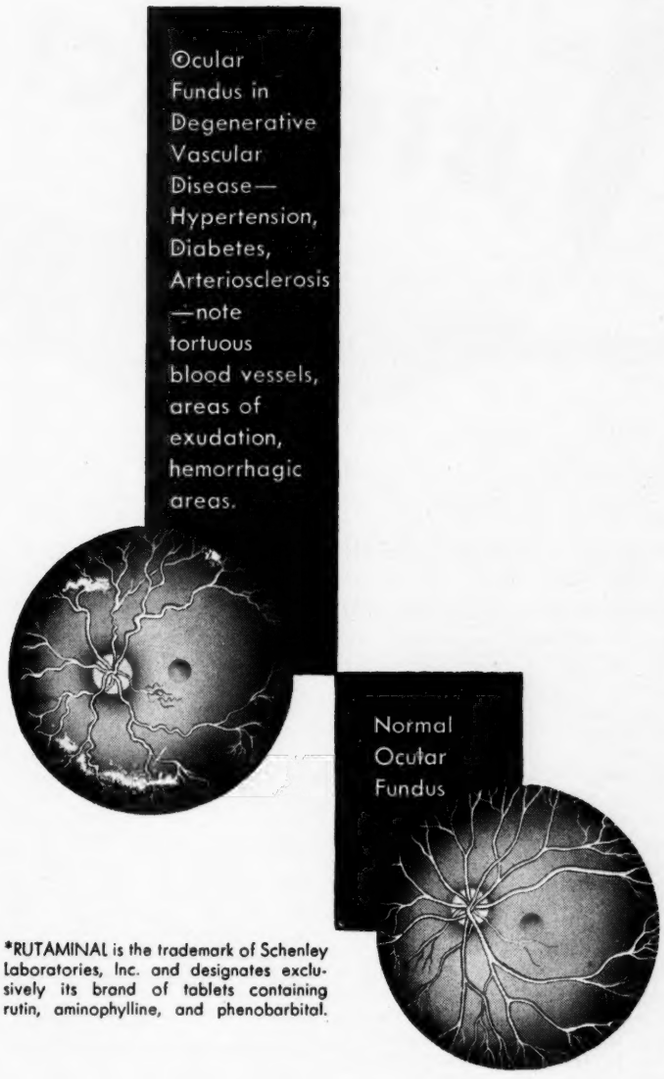

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1. Grimson, Marmont, Reardon and Hendrix: Ann. of Surg., 127: 5, May, 1948.
2. Reich, N. E.: Med. Times, Jan., 1949.

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